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ELECTRONYSTAGMOGRAPHIC FINDINGS IN MULTIPLE SCLEROSIS

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Abstract. Fifty MS cases were studied both clinically and by neuro-otological methods. MS diagnosis was verified using both Schumacher's criteria and cerebrospinal fluid (CSF) findings. Seventy-two per cent of the subjects were studied within the first 3 years after the appearance of the first possible anamnestic symptoms of the disease. Only 5 of the patients had suffered from MS for more than 13 years. Special emphasis was paid to those cases which came in for study at a relatively early stage of the disease. Either spontaneous or positional nystagmus was found in 60% of all cases. No significant hearing disturbances were found in our material. The present results suggest that electronystagmography and other neuro-otological techniques provide a valuable aid in the early differential diagnosis of MS because of their sensitivity and the close relationship between predilection sites of MS and those structures which contribute to the maintenance of balance.

Multiple sclerosis (MS) is the most common of the demyelinating diseases of the central nervous system. According to Panelius (1969) its prevalence in the southwestern part of Finland is 35.4 for 100 000 inhabitants. It is a well established fact that the disease lesions in multiple sclerosis (MS) are diffusively scattered throughout the white matter but at the same time there are also some predilection areas in the brain which often show clinical signs earlier than others. Such regions are, for example, the brain stem and optic nerves where slight morphological changes can actually lead to profound clinical manifestations (Lumsden, 1970). Although MS may begin with almost any neurological symptom vertigo and nystagmus are often mentioned as preliminary manifestations before verification of diagnosis in clinical studies (Müller 1949).

McAlpine et al. (1965) concludes that vestibular and auditory findings in MS are variable. The contradictory findings of different authors may be due to the fact that some investigators include among brain stem manifestations only those signs which are found at routine neurological examination. Differing results may therefore be expected in studies where more advanced methods, aimed at testing vestibular responses and nystagmus, are used. It must also be borne in mind that these findings are very difficult to interpret and it is therefore essential for clinical purposes to follow the changes in electronystagmographic findings during the various stages of the disease so that their significance as a diagnostic aid in demonstrating brain stem lesions may be evaluated, especially during the early stages of MS.

This study contains a report on the type and frequency of various neuro-otological findings in diagnosed MS cases. Special emphasis is given in this material to those MS cases who came under our care at a relatively early stage of the disease because it is often difficult to demonstrate changes at routine neurological examination.

MATERIAL AND METHODS

Patient material

The material consists of 50 patients who underwent neuro-otological examination for various reasons. MS diagnosis was made on the basis of Schumacher's criteria (Schumacher et al., 1965) for all patients. The major criteria in

tion-determined in 10 cases (Nylén's type II) and irregular direction-changing in 2 cases (Nylén's type III). Nystagmus was spontaneous in 17 cases. It is important to stress that hearing tests were normal. This shows that the peripheral part of the labyrinth system would give normal reactions by caloric irrigations. Despite this assumption it was found that caloric irritability was decreased in 18 cases, showing that MS affects the first neuron in the vestibular pathways more than neurons mediating purely auditive information. Directional preponderance was found in 14 cases.

The ocular fixation index was higher than 50% in 22 patients. (In other words the fixation did not suppress the caloric nystagmus as it would in normal subjects and those patients probably have a central lesion in the vestibular pathway.) Although all patients were asked to perform mental arithmetic in order to keep them awake dysrhythmic caloric reaction patterns were observed in 16 cases. This also suggests the presence of a central lesion in vestibular pathways either in the brain stem or at a higher central level.

Table II. *Neurological deficiency symptoms (cerebellar and brain stem symptoms, pyramidal signs, ocular muscle paresis and intranuclear ophthalmoplegy, facial abnormalities) and positive neuro-otological symptoms (positional nystagmus according to Nylén and spontaneous nystagmus)*

Total number of patients was 50

	No. of positive findings	Unilateral	Bilateral
Dysmetry	32	5	27
Dysdiadochokinesis	44	3	17
Ataxia	20		
Extensor plantar response	38	8	30
Ocular muscle paresis of intranuclear ophthalmoplegy	27		
Facial weakness or facial paresis	10	9	1
Positional nystagmus			
Nylén type I	4		
Nylén type II	10		
Nylén type III	2		
Spontaneous nystagmus	17		
Directional preponderance	14		
Hypoexcitability in caloric test	18		
OFI higher than 50 percent	22		

DISCUSSION

It is well established that clinical history, relapses, fluctuating course, disseminated neurological signs and positive CSF findings are all helpful in making MS diagnoses. There are, however, cases where differential diagnostic problems are extremely difficult. The present results show that involvement of the vestibular system and its central connections already exists at an early stage of the disease. We do not of course assume that positive findings in neuro-otological examination are alone sufficient to conclude that a patient is suffering from MS. However, when there are certain other scattered signs in the neurological examination, such as transient spinal level symptoms, optic neuritis, slight monoparesis, paraparesis and possibly also other findings suggesting that neurological lesions are outside the brain stem we may say that electronystagmographic examination is of real value in revealing a dysfunction in the vestibular system and its central connections. Detailed neuro-otological ex

Table I. *Age distribution, age at onset and time between onset of first symptoms and neuro-otological examination*

Total number of multiple sclerosis cases is 50 (23 males, average age of onset 34.3 years, 27 females average age of onset 32.3 years)

Age groups	Age distribution (no. of cases) at the age of examination	Age at onset (no. of cases)	Duration of illness before neuro-otological examination (years)	
15–25	4	7	0–2	14
26–35	17	19	2–3	22
36–45	23	22	3–4	5
46–55	4	2	4–5	2
56–65	2	0	5–6	1
			8–9	1
			over 13	5

amination seems to reveal disease affections in the brain stem earlier and more selectively than routine neurological examination. The significance of such things as facial asymmetry and nystagmus in different patient series are very difficult to evaluate and much will depend on the experience of the clinician in question. Facial weakness was found in 5% of the cases in our material. The corresponding figures in Kurtzke's material (1970 *a*) are 2.6% in Müller's material (1949) 11.0% and in Abb's material (Abb & Schaltenbrand, 1956) 14.4%. Nystagmus is one of the most common findings in MS. According to Abb & Schaltenbrand (1956) it is present in 40% of all cases and in Müller's material (1949) it was found in 17%. In our material the corresponding percentage was 60. The differences in these findings can easily be explained on the basis of the differences in the age distribution of the material and differences in the duration of the disease.

Vertigo is caused by a very complicated pattern of functional disturbances which include both complex peripheral vestibular and central functional lesions due to various disease processes. Vertigo is found frequently in the clinical history of MS patients and it seems to be one of the most common early manifestations (Müller 1949 Hahn et al. 1959). Seen against this background the results in the present study are very interesting for differential diagnostic purposes. They show that abnormalities in hearing are found only occasionally. If this can be confirmed for wider MS material, it will also help in the differential diagnosis of MS especially if at the same time the common brain stem symptoms caused by cerebrovascular lesions in the vertebro-basilary region are taken into account. As is well known, vascular lesions often cause disturbances in hearing which can be demonstrated by audiometry. The same is true of such tumours as acoustic neurinoma where the clinical picture may resemble brain stem multiple sclerosis. The differential diagnosis of cerebellar lesions and brain stem affections which are caused by various tumours are a difficult clinical problem and one must therefore always be extremely cautious when drawing conclusions. Exclusive neuroradiological examinations are often necessary in cases where there is a suspected clinical case history with increase of CSF proteins and positive neuro-otological findings, although no signs of increased intracranial pressure are demonstrable. From the clinical point of view vestibular neuronitis with acute onset is extremely difficult to distinguish from early MS because if in the former disease the question is one of brain stem encephalitis as is sometimes thought CSF findings may be sparse and very similar to those found in MS. In such cases, however electronystagmography will provide valuable additional information. In vestibular neuronitis it can be demonstrated by ENG that the disturbance is due to peripheral lesion and such lesions are not often seen in MS. Some authors, especially in earlier literature, have described hearing abnormalities in MS. The results derived from the present material, where MS diagnoses were established on the basis of generally accepted international criteria and where audiometry was also used as a differential diagnostic aid show that before CSF findings are included in MS series there may have been a number of cases giving an "atypical" picture of MS in which the diagnoses were wrong and loss of hearing due to some other reason. It is of course possible that in some MS cases central hearing loss may occur. The present material included five cases in which the duration of disease was more than 13 years in none of them, however was it possible to show any significant hearing abnormality. Present results therefore suggest that if central hearing abnormalities are found in detailed neuro-otological examination in an early stage of the disease process some other diagnosis than MS should be considered. Such neurological symptoms as dysarthria, intention tremor dysdiadocho-kinesia and ataxia are usually mentioned as symptoms of MS (Kurtzke 1970 *b*). These were also found in our material but it seems that positive electronystagmographic findings are a better indicator

of early stages of MS. In other words vestibular dysfunction in one form or another without defect in hearing together with slight or evident pathology in CSF immunoglobulins should lead the clinician to consider MS as an alternative diagnostic possibility even when there are no other clearly identifiable neurological signs. In such cases a continuous follow up of the patient, with the help of CSF tests and electronystagmographic techniques may provide the clinician with a valuable aid in what is often and exceedingly difficult diagnostic problem to demonstrate brain stem lesions.

ZUSAMMENFASSUNG

60 Fälle von MS wurden sowohl mit klinischen als neuro-otologischen Methoden untersucht. MS-Diagnose wurde durch Anwendung von sowohl Schumachers Kriterium als cerebrospinale Flüssigkeitsfunde verifiziert. 72% von den Subjekten wurden innerhalb der ersten 3 Jahre nach Erscheinung der ersten wahrscheinlichen anamnestischen Krankheitssymptome studiert. Nur fünf Patienten hatten an MS mehr als 13 Jahre gelitten. Besonders große Bedeutung wurde denjenigen Fällen gegeben, die in einem relativ frühen Stadium der Krankheit zur Untersuchung einkamen. Entweder spontanes oder positionales Nystagmus war in 60% aller Falle zu finden. Keine signifikative Hörstörungen wurden in unserem Material gefunden.

Die vorliegenden Resultate geben an, daß Elektronystagmus und übrige neuro-otologische technische Methoden wertvolle Hilfe in der frühen differentialen Diagnose von MS infolge ihrer Empfindlichkeit und nahe Verwandtschaft zwischen dem Prädilektions Gebiet von MS und denjenigen Strukturen, die an der Aufrechterhaltung der Balance teilnehmen, geben.

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SEPARATE RECORDING OF THE MOVEMENTS OF THE HUMAN EYES DURING PARALLEL SWING TESTS

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Abstract In parallel swing tests different eye tracks were recorded. The eye movements of both eyes do not always seem to be related to one another In some positions only one eye was moving. Sometimes the eye movements showed double the swing frequency For this phenomenon a possible explanation is given.

In the literature concerning parallel swing it is generally accepted that both eyes react com pletely *identically upon linear acceleration* stimuli. In reality however the eye movements have practically never been recorded sepa rately Only in rabbits have separate eye movements been recorded, and under certain conditions different eye tracks have been obtained. The present tests were made in an effort to determine whether or not the two human eyes follow an exactly identical pattern of movements when being stimulated on the parallel swing.

METHOD

The parallel swing used in these investigations had a period of 3 3 sec, and the amplitude used was about 30 cm. In order to avoid minor shiftings of the skin of the head with respect to the skull during the swinging process, on the parallel swing a second small parallel swing was mounted on which the test subjects rested their heads. The length of the cords of this second swing was 50 cm (Fig 1)

Because the mass of the head was much greater than that of the swing on which it rested, every possible movement was definitel prevented. This is very important, since mino shiftings of the electrodes may result in rathe large signals which may easily lead to fals interpretations. For the recording of the ey movements seven electrodes were used whic were fixed in position as sketched (Fig. 2).

An eighth electrode was fixed on the wris

Recordings were made as follows. Right eye D–E, called "vertical" in text, (A–C) + β(D + E), called horizontal" in text. Left eye: F- G called vertical" (C–B + γ(F–G) calle "horizontal"

In the test procedure the gain factors β an γ were adjusted in such a way that vertical ey movements were no longer perceptible on th horizontal recordings. This effect was near always achieved.

In total 22 subjects have been tested on the swing. They were moved lengthwise in the fol lowing positions: 1) lying on the back 2) lying on the right side and 3) lying on the left side. Each subject was instructed to keep his eyes closed and to assume a reverie state as far as possible.

RESULTS

Lying on the back Sinusoidal horizontal eye movements were observed in 6 subjects. Out of these 6, 2 showed a sinusoid with double the *swing frequency* (Fig 3). Attention is

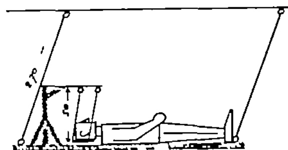


Fig 1

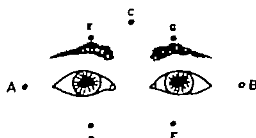


Fig 2

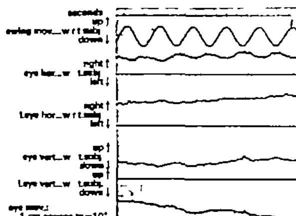


Fig 4

drawn to the opposite direction of the movements. In two other cases vertical identical eye movements were observed.

Lying on the right side· Only in 1 subject were vertical eye movements observed, whereas 15 subjects showed horizontal sinusoids. In this group 6 subjects were found in which only the right eye produced a sinusoidal pattern (Fig. 4).

Lying on the left side In 14 subjects, horizontal sinusoids were observed. Six subjects moved only the left eye. Moreover 11 subjects produced also vertical movements with the left eye (Fig. 5).

In all cases the phase differences between the eye movements and the swing movements varied among the subjects from −180 to +180

A remarkable case is that of a man with right-sided labyrinthine dysfunction. After swinging on the left side it was observed that, while lying on the right side before swinging, the right eye produced sinusoids with about the same frequency as the swing frequency (Fig. 6).

DISCUSSION

In some cases the sinusoidal eye movements began only after 4 minutes of constant ampli-

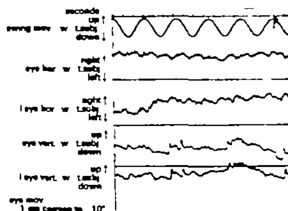


Fig 3

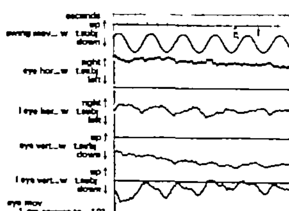


Fig 5

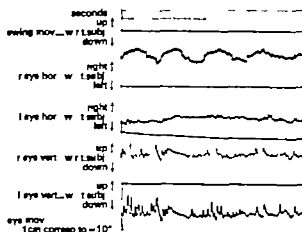


Fig 6

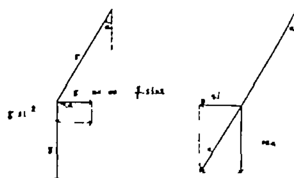


Fig 8

tude swinging. It is concluded, therefore that faulty measurement techniques were definitely not the source of the signals measured.

There are some indications that a vestibular system under pressure reacts more intensively The pressure on the underlying labyrinth is approximately 13 cm H_2O higher than on the upper labyrinth. The eye movements are known to be more closely linked to the homolateral labyrinth. This is a possible explanation for the larger excursions of the underlying eye

The occurrence of double the swing frequency may be the result of the vertical oscillat_ movements of the swing An analysis shows t if we portray the otoliths schematically as in *Fig. 7 they are subjected to the following* accelerations as a result of the swing movements.

If $\alpha(t) = \alpha_m \cos \omega t$ we use the following approximations because α_m is very small

$\sin (\alpha_m \cos \omega t) \simeq \alpha_m \cos \omega t$

$$\cos (\alpha_m \cos \omega t) \sim \sqrt{1 - \alpha_m^2 \cos^2 \omega t}$$

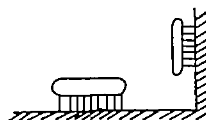


Fig 7

If $\omega_h = \frac{d\alpha}{dt} = \omega \alpha_m \sin \omega t \rightarrow a_r = \omega_h^2 r = \left(\frac{d\alpha}{dt}\right) r^2$
$= \omega^2 \alpha_m^2 r \sin^2 \omega t$

Hor acc: $-g/2. \sin 2\alpha - a_r \sin \alpha = -g\alpha_m \cos \omega t - r\omega^2 \alpha_m^2 \sin^2 \omega t \cos \omega t$

Because $\alpha = 0\ 12$ rad $\omega = 2$ Hz, $r = 2.5$ m, the acceleration is $-1.2 \cos \omega t - 0\ 02 \sin^2 \omega t \cos \omega t \simeq -1\ 2 \cos \omega t$

Vert acc: $-g \sin^2 \alpha + a_r \cos \alpha = -g\ \alpha_m^2 \cos^2 \omega t + r\omega^2 \alpha_m^2 \sin^2 \omega t \sqrt{1 - \alpha_m^2 \cos^2 \omega t}$
$\rightarrow -0\ 14 \cos^2 \omega t + 0\ 14 \sin^2 \omega t = -0\ 14 \cos 2\omega t$

This maximal vertical acceleration of 14 cm sec^2 exceeds the generally agreed minimum perceptible acceleration.

CONCLUSIONS

1 For the swing acceleration of 120 cm/sec not all the subjects showed a response.

2. In the side positions the response was no the same for both eyes. In cases where only one eye responded it was always the lower eye

3 Several instances occurred in which the response was of twice the frequency of the swing Dynamic mechanical analysis indicate that this response may be the result of the vertical accelerations of the parallel swing.

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We thank Miss Anneke Matthijs for her administrative assistance and Mr S G Mey and Mr A. M Sad for their valuable technical help.

ZUSAMMENFASSUNG

In Parallelschaukel Tests sind ungleiche Augenbewegungen registriert worden. Die Bewegungen von beiden Augen scheinen nicht immer miteinander übereinzustimmen. Es gab Positionen, in denen nur ein Auge sich bewegte. Manchmal war die Frequenz der Augenbewegung zweimal so gross wie die der Schaukel. Für dieses Phänomen ist eine mögliche Erklärung gegeben worden.

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REVISED NORMATIVE STANDARDS OF PERFORMANCE OF MEN ON A QUANTITATIVE ATAXIA TEST BATTERY

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Abstract Revised normative standards of performance are presented, of men, ages 16–60 years, on a quantitative ataxia test battery in terms of five new chronological age groupings based on a sample of 1 055 normal men. Very nearly similar sensitivity of all battery subtests to aging influences was observed, which implies a unitary sensitivity of the battery to such influences on the complex postural equilibrium functions sampled by it. Results tentatively suggest that the progressive nature of negative aging influences along the life span sampled become apparent several years earlier than reported previously The new normative standards should allow more precise laboratory and clinical applications of the test battery which has proved to be useful particularly in the vestibular physiological and neuro-otological assessment of postural equilibrium-disequilibrium, including spontaneous and induced vestibular ataxia. The test battery has other clinical and research applications.

Several years ago age-influenced normative *standards of performance on a new quantitative* ataxia test battery designed initially for assessment of vestibular ataxia (Fregly in press; Graybiel & Fregly 1966)[1] were published (Fregly & Graybiel, 1970 Graybiel & Fregly 1966). To control for the observed negative influence of chronological aging on scores, the normative standards were presented in relation to several chronological age groupings. Meanwhile, many additional individuals—almost entirely men—were tested, and new indications of aging influences on test scores came to light. Accordingly normative standards were revised in terms of new chronological age groupings, incorporating the additional samples of normal men tested and new 5th percentile *and below cut-off scores relative to an arbitrary* definition of frank ataxia (Fregly & Graybiel, 1970 Fregly et al. 1971). This up-dated information is presented and discussed to allow more precise laboratory and clinical applications of the test battery

PROCEDURE

Subjects

The sample of 1 055 normal men, 16 to 60 years of age included all those physically fit[2] *who had been tested since standardization of* the short version of the "rail battery" and the "floor battery" of ataxia tests (Fregly in press; Fregly et al. 1971 Graybiel & Fregly 1966). Occupational groups included experienced and student military and civilian aviators; Army and Navy enlisted and civilian college student volunteer research subjects; Navy deep-sea divers and miscellaneous active and retired

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Opinions or conclusions contained in this report are those of the authors and do not necessarily reflect the views or endorsement of the Navy Department.

[1] The items of the battery are also known as tests of postural equilibrium–disequilibrium (Graybiel & Fregly 1966)

[2] All had undergone a comprehensive medical and audiological evaluation. The very great majority also had benefit of a comprehensive vestibular evaluation.

Table I *Correlation of ataxia test battery scores with chronological ages of normal men*

Ataxia test battery	Age categories 16–60		16–30		31–40		41–45		46–50		51–60	
	N	*r*	*N*	*r*	*N*	*r*	*N*	*r*	*N*	*r*	*N*	*r*
SR	1 055	297*	547	031	100	076	125	041	241	044	42	024
Walk E/0	1 055	300*	547	087	100	172	125	078	241	047	42	085
Stand E/0	1 055	266*	547	058	100	186	125	080	241	018	42	014
Stand E/C	1 055	363*	547	098	100	149	125	168	241	082	42	048
SOLEC-R	749	413	488	061	85	126	36	287	105	029	35	168
SOLEC-L	749	308*	488	039	85	061	36	098	105	100	35	159

$p < 0.001$

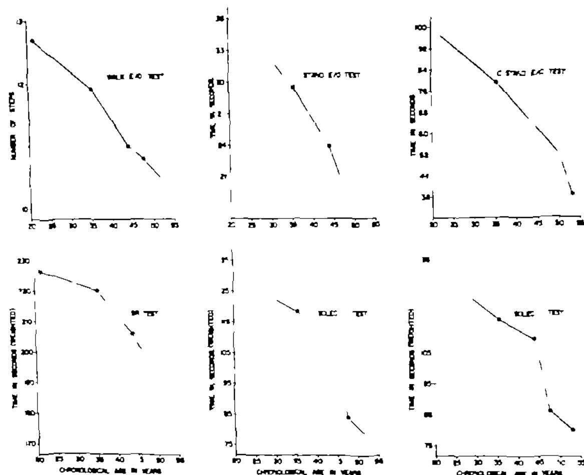


Fig. 1 Chronological aging influences on ataxia test battery performance scores. (*A*) Walking heel-to-toe with eyes open on a 3/4-inch-wide, 8-foot-long rail. (*B*) Standing heel-to-toe with eyes open on the 3/4-inch-wide rail. (*C*) Standing heel-to-toe with eyes closed on a 2 1/4-inch-wide, 30-inch-long rail. (*D*) Sharpened Romberg: standing heel to-toe on the floor with eyes closed. (*E–F*) Stand One Leg Eyes Closed-Right and -Left on the floor

Table II *Walk E/O test Norms, means and standard deviations of scores of normal men in five age categories*

Percentile	Age categories 16–30	31–40	41–45	46–50	51–60
99th	15	15	15	15	15
95th	—	—	—	—	—
90th	—	—	—	—	14
85th	—	—	14	14	—
80th	—	—	13	13	13
75th	—	14	—	—	—
70th	—	—	—	—	12
65th	14	—	12	—	11
60th	—	13	—	1	—
55th	—	—	—	—	10
50th	13	—	11	11	—
45th	—	12	—	—	—
40th	—	—	10	10	—
35th	12	11	—	—	9
30th	—	10	—	9	—
25th	11	—	9	—	8
20th	—	—	—	8	—
15th	10	9	8	7	7
10th	9	7	7	—	—
5th	8	6	6	5	—
4th	7	—	—	—	—
3rd	—	—	—	—	—
2nd	—	4	5	4	4
1st	6	—	—	—	—
Age, *N*	547	100	1[illegible]5	[illegible]41	42
Mean	21 43	35.52	44 00	47 65	5[illegible].98
S.D	3.[illegible]4	3.01	1 12	1.36	2.01
Score (maximum 15 steps)					
Mean	12.69	11.89	11.00	10.83	10.38
S D	2.42	2.82	2.66	2.99	2.71

Table III *Stand E/O test Norms, means, and standard deviations of scores of normal men in five age categories*

Percentile	Age categories 16–30	31–40	41–45	46–50	51–60
99th	166	173	107	76	41
98th	148	143	100	68	39
97th	130	113	79	55	38
96th	118	93	73	49	37
95th	105	78	67	43	36
90th	72	63	45	35	28
85th	53	48	37	27	[illegible]6
80th	47	37	32	4	25
75th	4	3[illegible]	29	[illegible]2	23
70th	38	29	26	1	22
65th	34	27	24	20	21
60th	31	[illegible]5	2[illegible]	19	20
55th	29	[illegible]3	20	18	19
50th	27	21	18	17	18
45th	26	19	17	16	17
40th	24	18	16	15	16
35th	22	17	14	14	15
30th	[illegible]0	16	13	13	13
25th	19	15	1	12	12
20th	17	13	11	11	11
15th	16	12	10	—	10
10th	14	10	9	10	9
5th	1[illegible]	9	8	9	8
4th	11	8	—	—	—
3rd	10	—	7	8	—
2nd	9	6	5	—	7
1st	—	3	4	—	[illegible]
Age, *N*	547	100	1[illegible]5	41	42
Mean	21 43	35.52	44 00	47 65	52.98
S D	3.[illegible]4	3.01	1 1[illegible]	1.36	[illegible]04
Score (maximum 180 seconds)					
Mean	36.35	29.50	[illegible]3.88	19.90	18.12
S.D	30.24	28 73	19 47	14 66	7.59

military and civilian scientific, medical engineering aviation and technical personnel.

Method

Because detailed administration and scoring procedures have been published previously (Fregly in press, Fregly & Graybiel, 1968 Fregly et al., 1971 Graybiel & Fregly 1966) these tests are described only briefly below. All tests were undertaken while subjects wore hard-soled shoes and were in the stringent position of arms folded against chest, feet aligned heel-to-toe (tandemly), with the exception of the Stand One Leg Eyes Closed tests, and body erect or nearly erect. Administered in the following order they consisted of the

1 Sharpened Romberg (SR) standing on floor with eyes closed for 60 seconds. M imum score obtainable. 240 seconds.
2. Walk Eyes Open (Walk E/O) walkin steps per trial on a 3/4-inch-wide by 8-fo long rail. Maximum score obtainable: steps.
3 Stand Eyes Open (Stand E/O) standing the 3/4-inch-wide rail for a maximum 60 seconds per trial. Maximum score obta able 180 seconds.
4 Stand Eyes Closed (Stand E/C) standing

Table IV *Stand E/C test Norms, means, and standard deviations of scores of normal men in five age categories*

	Age categories				
Percentile	16–30	31–40	41–45	46–50	51–60
99th	180	180	180	180	121
98th	—	—	—	—	119
97th	—	—	—	—	102
96th	—	—	179	179	101
95th	—	—	—	165	100
90th	—	179	152	135	82
85th	178	163	131	93	75
80th	163	148	120	75	51
75th	150	127	97	65	44
70th	140	118	72	54	37
65th	127	100	62	48	35
60th	115	78	56	43	33
55th	106	63	47	39	31
50th	97	56	43	34	30
45th	78	49	37	29	28
40th	70	45	34	28	26
35th	62	36	30	25	25
30th	55	32	27	23	23
25th	48	29	24	21	21
20th	43	26	21	20	19
15th	35	23	19	18	17
10th	30	20	17	16	14
5th	22	16	13	14	11
4th	20	15	12	13	10
3rd	18	14	11	—	—
2nd	16	—	10	11	9
1st	14	—	9	10	—
Age, *N*	547	100	125	241	42
Mean	21.43	35.52	44.00	47.65	57.98
S.D	3.24	3.01	1.12	1.36	2.01
Score (maximum 180 seconds)					
Mean	98.01	79.29	63.57	51.37	37.50
S.D	55.32	58.03	51.89	44.84	26.86

Table V *SR test Norms, means, and standard deviations of scores of normal men in five age categories*

	Age categories				
Percentile	16–30	31–40	41–45	46–50	51–60
99th	240	240	240	240	240
95th	—	—	—	—	—
90th	—	—	—	—	—
85th	—	—	—	—	—
80th	—	—	—	—	—
75th	—	—	—	—	—
70th	—	—	—	—	239
65th	—	—	—	—	—
60th	—	—	—	239	238
55th	—	—	—	—	223
50th	—	239	239	238	208
45th	—	—	—	211	198
40th	239	—	238	195	192
35th	—	238	—	187	186
30th	—	—	207	183	146
25th	238	221	191	157	134
20th	228	212	183	143	105
15th	202	205	135	106	76
10th	189	158	92	68	69
5th	161	105	64	39	28
4th	145	95	58	31	27
3rd	134	83	42	26	26
2nd	96	80	35	23	25
1st	55	50	29	17	4
Age, *N*	547	100	125	241	42
Mean	21.43	35.52	44.00	47.65	52.98
S.D	3.24	3.01	1.1	1.36	2.01
Score (maximum 240 seconds)					
Mean	226.70	220.33	205.95	190.29	181.00
S.D	33.95	42.57	59.77	67.36	71.62

a 2¼-inch-wide by 30-inch-long rail for a maximum of 60 seconds per trial. Maximum score obtainable 180 seconds.

5 and 6. Stand One Leg Eyes Closed (SOLEC-R and SOLEC-L): standing stationary on the floor on each leg for a maximum of 30 seconds on any trial. Maximum score obtainable 150 seconds on each leg.

7 Walk On Floor Eyes Closed (WOFEC): walking in the stringent position described above for a maximum of 10 steps per trial. Maximum score obtainable 30 steps.

This battery of ataxia tests evolved in stages. Whereas all subjects undertook the "rail battery" and the SR test, as noted above, a smaller number also undertook the SOLEC tests (*N* 749) and fewer still also undertook the WOFEC (*N* 287).

RESULTS

Chronological age influences on ataxia test battery scores

To control for the negative influences of chronological aging on performance it was necessary to demonstrate a nonsignificant correlation between chronological age and scores on each of the test battery items within each of several age groupings. Five age groups were found to be required to accomplish this end, as shown in Table I. The mean ataxia test

Table VI. *SOLEC R test. Norms, means, and standard deviations of scores or normal men in five age categories*

	Age categories				
Percentile	16–30	31–40	41–45	46–50	51–60
99th	150	150	150	150	150
95th	—	—	—	—	—
90th	—	—	—	—	149
85th	—	—	—	149	131
80th	—	—	—	138	128
75th	—	—	—	127	114
70th	—	—	149	124	111
65th	—	—	—	117	102
60th	149	149	148	105	90
55th	—	148	145	87	79
50th	148	147	135	77	69
45th	146	140	128	71	59
40th	141	128	115	65	55
35th	133	112	106	49	49
30th	129	100	72	43	44
25th	124	91	65	37	40
20th	115	78	56	34	33
15th	95	62	45	30	29
10th	75	37	39	27	24
5th	54	31	22	23	17
4th	50	30	20	22	16
3rd	44	29	18	20	—
2nd	39	—	17	18	15
1st	34	27	15	11	14
Age, *N*	488	85	36	105	35
Mean	21.25	35.71	43.75	47.83	53.14
S.D	3.10	2.95	1.42	1.43	2.11
Score (maximum 150 seconds)					
Mean	129.87	118.39	110.53	83.91	76.77
S.D	31.68	4[illegible].02	46.61	46.93	43.61

Table VII. *SOLEC L test. Norms, means and standard deviations of scores of normal men in five age categories*

	Age categories				
Percentile	16–30	31–40	41–45	46–50	51–60
99th	150	150	150	150	150
95th	—	—	—	—	—
90th	—	—	—	—	149
85th	—	—	—	149	137
80th	—	—	—	140	12[illegible]
75th	—	—	—	129	123
70th	—	149	149	125	110
65th	—	148	148	118	101
60th	—	145	146	110	95
55th	—	139	141	97	74
50th	149	130	138	84	70
45th	148	127	133	71	67
40th	142	123	125	57	60
35th	133	114	101	52	56
30th	127	100	85	48	45
25th	122	91	65	4	41
20th	113	68	53	38	38
15th	98	60	41	34	34
10th	78	44	22	27	29
5th	56	37	19	22	17
4th	53	35	—	20	16
3rd	42	34	18	18	—
2nd	31	31	12	16	15
1st	24	22	10	13	14
Age, *N*	488	85	36	105	35
Mean	21.25	35.71	43.75	47.83	53.14
S.D	3.10	2.95	1.42	1.43	2.11
Score (maximum 150 seconds)					
Mean	130.12	115.55	109.26	86.17	80.26
S.D	31.70	40.23	48.86	46.69	43.51

scores within each new chronological grouping are plotted in Fig. 1.[1] It may be seen in Table I that in the total group of subjects tested (16–60 year olds) all correlations between chronological age and subtest scores were highly significant, whereas none of the consistently lower correlations within the five subgroups were statistically significant.

Revised ataxia test battery normative standards

Mean ataxia test battery subtest scores and standard deviations, and the raw scores and their percentile equivalents for each of the five new chronological age groupings are shown in Tables II to VII. Included in each table are the mean ages and standard deviations. For the convenience of users of the ataxia test battery the recently published WOFEC *test norms* (Fregly et al., 1971) are reproduced in form similar to the above in Table VIII. Also for convenience sake, all scores arbitrarily defined as "ataxic" (Fregly & Graybiel 1970, Fregly et al. 1971) i.e., all 5th percentile and below cut-off scores (4th percentile and below for WOFEC) on each ataxia test battery item for each of the five chronological age groupings, are set off by a line between the 10th and 5th percentile in Tables II to VII. It should be emphasized, as

[1] WOFEC scores by ages are not included because of their very low and not statistically significant correlation (r 0.06) with age (17–61 year old men) (Fregly et al., 1971).

Table VIII. *WOFEC test Norms mean, and standard deviation of scores of normal men, ages 17–61 years*

Percentile	Score
99th	30
95th	—
90th	—
85th	—
80th	—
75th	—
70th	—
65th	—
60th	—
55th	—
50th	—
45th	—
40th	—
35th	—
30th	—
25th	—
20th	—
15th	—
10th	—
5th	—
4th	29
3rd	27
2nd	24
1st	17
Age, *N*	287
Mean	24 25
S D.	8.73
Score (maximum 30 steps)	
Mean	29 74
S.D	1.65

reported previously (Fregly & Graybiel, 1970 Fregly et al., 1971) that, whereas a raw score having a 5th percentile, or below equivalent has been defined as an ataxic test score, an individual is considered by us to be frankly ataxic (Fregly et al., 1971) only when scores on all items of the battery performed with eyes closed (Stand E/C, SR, SOLEC R and SOLEC L, and WOFEC) fall at or below the 5th per centile level (4th percentile for WOFEC indicated by dotted line in Table VIII,[1] and then only after "testing the limits"[2] (Fregly et al., 1971).

[1] A perfect score of 30 steps was obtained by 96% of the standardization group and, therefore, has a 100th-5th percentile equivalent (Fregly et al., 1971).

[2] This refers to retesting an individual to insure the reliability of 5th percentile or below scores obtained during initial testing.

[3] A determination of expected medical and other health-related correlates of aging by data analysis of carefully evaluated variables would undoubtedly throw desirable light on the nature of the observed group differences in terms other than aging per se; e.g. in terms of physiological aging Preliminary efforts in this direction have begun (Fregly et al., 1968 Fregly et al., 1972).

COMMENT

Previously published normative standards of performance on all subtests of the "rail battery" (Graybiel & Fregly 1966) and on all subtests (except WOFEC) of the "floor battery" (Fregly & Graybiel, 1968) were based on the following chronological age groupings. 17–42, 43–50 and 51–53 years. The new chronological age groupings on which the revised normative standards are based tentatively suggest that aging[3] negatively influences ataxia test battery performance skills several years earlier than previously reported (Fregly & Graybiel, 1968 Graybiel & Fregly 1966)· i.e., within the 30–40 rather than 43–50 year age range.

Noteworthy is the finding that amidst great individual differences in the performance scores of the men tested (Tables II to VII as well as amidst differences in the nature of the complex performance skills sampled by the varied subtests, the magnitude of the negative influences of aging observed on all subtests (except WOFEC) performance scores was very nearly similar (Fig. 1). This result implies a reliably unitary sensitivity of the ataxia test battery to aging influences on the complex postural equilibrium functions sampled by it. However the ultimate reliability of all chronological age group differences in performance scores on this ataxia battery awaits testing of additional samples of comparable individuals (particularly in the 51–60 age group).

A revision of normative standards of ataxia test battery performance scores of samples of women is needed also, particularly for clinical purposes, and awaits availability of larger samples of testees who are comparable to the samples of men tested in terms of medical and physical status. Meanwhile, present revised

normative standards based on new chronological age groupings of the maximum number of normal men tested to date at this laboratory which are now more nearly similar to the chronological age groupings employed for women—ages 18–29 30–49 and 50–59 (Fregly & Graybiel 1968 Graybiel & Fregly 1966)—should allow greater comparability of the scores of men with those of women, as well as generally more precise application of the test battery in both laboratory and clinical situations. It has proved to be particularly useful in vestibular physiological and neuro-otological assessment of postural equilibrium-disequilibrium including spontaneous and induced vestibular ataxia (Fregly in press Fregly & Graybiel, 1968 Fregly & Graybiel, 1970 Fregly et al. 1971 Graybiel & Fregly 1966) Other clinical and/or research applications of the battery such as general medical, physiological pharmacological, gerontological, audiological, and psychological are recommended

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ZUSAMMENFASSUNG

Revidierte normative Leistungsziffern männlicher Versuchspersonen im Alter von 16–60 Jahren werden hier vorgelegt, die sich auf eine quantitative Ataxie Testserie an 1 055 normalen Versuchspersonen aufgeteilt in fünf neue Altersgruppen beziehen. In allen Teiltesten der Serie wurde eine sehr ähnliche Empfindlichkeit für Alterseinflüsse beobachtet, welche eine gleichförmige Reaktion der komplexen Gleichgewichtsfunktion der Körperhaltung auf solche Einflüsse belegt. Die Ergebnisse scheinen anzudeuten, dass Progressivität des gefundenen negativen Alterseinfl ses im Leben früher erscheint als bisher angenomm Die neuen normativen Ziffern müssten eine präzis Anwendung der Testserie in Klinik und Labor er ben. Die Serie hat sich für die vestibulär-physio gische und neuro-otologische Beurteilung des Glei und Nichtgleichgewichts der Körperhaltung einschli lich der spontanen und induzierten vestibulären At als besonders nützlich erwiesen. Die Testserie hat a auch andere Verwendungsmöglichkeiten im klinisch Bereich und in der Forschung.

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INTERACTION BETWEEN THE UTRICLES AND THE HORIZONTAL SEMICIRCULAR CANALS

I. *Unilateral Selective Sectioning of the Horizontal Ampullar Nerve followed by Tilting around the Longitudinal Axis*

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Abstract Selective unilateral sectioning of the horizontal ampullar nerve was performed in 48 cats. This resulted in horizontal nystagmus in a contralateral direction. The animals were then tilted around their longitudinal axis, and the effect on nystagmus was studied by visual inspection and electronystagmography If the cat was tilted to the operated side the nystagmus increased in frequency whereas if it was tilted to the opposite side the nystagmus frequency decreased. The cause of this is discussed.

In studying the function of the vestibular organ, the two systems, the semicircular canals and otolith organs, have usually been investigated separately The semicircular canals are known to react to angular acceleration and also to release nystagmus, whereas the otolith organs are influenced by linear acceleration (Löwenstein, 1956 Tait & McNally 1934) Opinions differ however regarding the effect which the otolith organs have on the eye movements. Some authors consider that they cause only eye deviations (Versteegh, 1927 Ulrich, 1934 Szentágothai, 1952, Jongkees, 1950) other authors maintain that they can also release nystagmus (Fernández et al., 1959 Owada et al. 1960). This problem is intimately connected with another phenomenon, frequently observed in otolaryngology namely positional nystagmus (Bárány 1921) The problem remained unsolved, however owing to the fact that the more precise influence of the otolith organs on the different eye muscles was still not known a few years ago Fluur & Mellström (1970) have studied these problems in the cat, and have shown, with regard to the horizontal eye movements, with which this paper deals, that on the lateral part of the utricle there is an area which, during electrical stimulation, causes a horizontal eye deviation to the stimulated side. In some of the cases, however nystagmus towards the same side was also released. Consequently the results are somewhat contradictory and we do not consider the problem concerning the horizontal eye movement representation on the utricular surface as definitely solved. The question is now whether the nystagmus may depend on the fact that the stimulation current extended to the horizontal canal or that it was elicited from the utricle itself We have therefore with another stimulation technique studied in a series of experiments, whether there is some interplay between the horizontal canal and the utricle. This paper describes how a destruction nystagmus, after unilateral selective sectioning of the horizontal ampullar nerves, is influenced by a change in the utricular activity caused by tilting along the longitudinal axis of the animal.

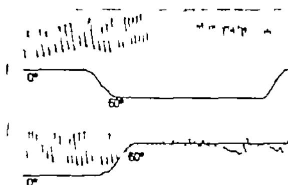


Fig 1 Consecutive curves from a cat after selective unilateral sectioning of the left horizontal ampullar nerve, followed by tilting. The upper curve shows the electronystagmography and the lower curve shows the tilting of the table. Tilting to the right upwards, to the left downwards.

MATERIAL AND METHODS

For the experiments 48 adult cats were used. They were anesthetized with ether with a so-called Ayer system, which is employed in pediatric anesthesia. The animals were placed on a tilting table which can be tilted around different axes.

A 3 cm long vertical incision was made im- y anterior to the external ear The ous external meatus was dissected free and cut close to the temporal bone, where after it was attached to the side by a selfretracting forceps. The middle ear was explored and the malleus, incus and the tensor tympani muscle were removed. The facial canal was opened and part of the nerve resected. At the bottom of the canal two small bluish spots were visible, marking the ampullae of the horizontal and the anterior vertical canals. Medial to these a fenestration was performed large enough for the visualization of the nerves from the two ampullae The horizontal ampullar nerve was finally cut as far away from the ampulla as possible. Great care must be taken not to damage the membranous labyrinth or the ampullae, or the utricle behind. However under the microscope it was not so difficult, since it was possible to see all the other structures and their borders and afterwards to check by visual inspection

The recording of the eye movements was done partly by direct visual ocular inspection of the cat's eyes, and partly by traditional electronystagmography with needle electrodes in the lateral canthi bilaterally and with the ground electrode in the skin of the neck.

Stimulation was applied by tilting the animals 60° around their longitudinal axis to either side

RESULTS

In order to avoid all conceivable artefacts, the operation was performed in stages. Five cats were wakened after a short period of anesthesia without any operation being performed The cat was then again anesthetized, and the middle ear explored. The animals were brought to a level of superficial anesthesia. Thereafter deep anesthesia was again induced and fenestration was performed but the horizontal ampullar nerve was not divided. Nystagmus did not develop in the cats at any of these stages when the animals were brought to a superficial level of anesthesia. Finally the horizontal ampullar nerve was selectively sectioned, and horizontal destruction nystagmus occurred towards the opposite side when the cats were brought to a level of superficial anesthesia.

In 16 cats tilting toward the operated side resulted in an evident increase in the frequency of nystagmus amounting to 1–10 beats/10 sec. Furthermore, where the beats had previously been somewhat irregular in shape, they now became much more regular in both frequency and amplitude On tilting toward the nonoperated side, 14 showed a decrease in nystagmus frequency of 1–8 beats/10 sec, and in 4 cats there was immediate total inhibition of nystagmus. Eight cats showed no substantial alteration in the character of the nystagmus during tilting toward the operated side, and 10 cats when tilted toward the nonoperated side. Twelve cats showed an "ideal" reaction when

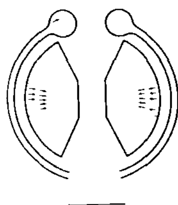


Fig 2.

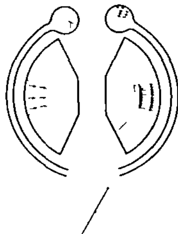


Fig. 3

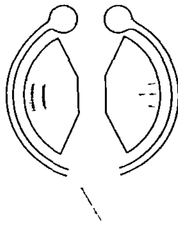


Fig. 4.

Fig 2. Schematic picture of the utricles and horizontal semicircular canals in resting position. The arrows indicate the orientation of the haircells, i.e., the direction in which they increase their discharge frequency

Fig 3. Schematic picture of the utricles and horizontal semicircular canals, after unilateral selective sectioning of the left horizontal ampullar nerve, and when the animal is tilted to the left. Arrow indication same as in Fig. 2. The number of arrows symbolizes discharge frequency

Fig 4. Schematic picture of the utricles and horizontal semicircular canals, after unilateral selective sectioning of the left horizontal ampullar nerve, and when the animal is tilted to the right. Arrow indication same as in Fig. 2. The number of arrows symbolizes discharge frequency

tilted in either direction i.e. facilitation during tilting toward the operated ear and inhibition toward the nonoperated side (Fig. 1).

DISCUSSION

The aim of this investivation was to create a system with a functioning reflex arc only from one horizontal semicircular canal, whose activity could then be so modulated by tilting the animal that the utricular activity increased on one side and simultaneously decreased on the other. The investigation has shown that tilting changes the nystagmus by either increasing or decreasing it, depending on the position. Fluur & Mellström (1970) have shown that horizontal eye movements from the otolith organs can be induced only by stimulation of a small utricular area situated in the middle of its lateral section (Fig. 2). It must be this area which influences the activity of the canal or the reflex arc, and causes the character of the nystagmus to change.

With the aid of a few figures we shall try to explain the course of events in the different situations. Fig. 2 shows the two semicircular canals and utriculi, and the direction in which the haircells in the two systems are oriented, i.e. *the direction in which they bend when the* activity increases. This is the resting position. If the cat is now tilted to the operated side, the activity is inhibited in the utricular area on that side, whereas, on the other side it is simultaneously increased. (Fig. 3). The effect on nystagmus may be due to the fact that the intact semicircular reflex arc is facilitated either by increased activity in the ipsilateral utriculus or by inhibition from the contralateral utriculus. This investigation does not enable us to determine which of these alternatives is operative.

If on the other hand, the animal is tilted to the nonoperated side the result is quite the opposite (Fig 4). Here, we have an increased activity in the utricle on the operated side, and inhibition on the other. As the investigation has shown, the effect on nystagmus is also the opposite.

Consequently the investigation has raised two new questions Are the results actually due to the utricular influence, as has been assumed in the discussion and in that case does the reaction originate from the ipsilateral or the contralateral utricle. These questions will be fully dealt with in a later paper

ZUSAMMENFASSUNG

Bei 48 Katzen wurde der horizontale Ampullarnerv unilateral abgeschnitten. Das resultierte in einem horizontalen Nystagmus nach die kontralateralen Seite. Danach wurden die Katzen um die longitudinelle Achse gedreht, und die Wirkung auf den Nystagmus wurde mit visueller Inspektion und Elektronystagmographie studiert. Wurden die Katzen nach der operierten Seite gekippt, erhöhte sich die Geschwindigkeit des Nystagmus wenn sie nach der anderen Seite gedreht wurden, stellte man eine Verminderung der Nystagmusgeschwindigkeit fest. Die Ursache darn wurde diskutiert.

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NYSTAGMUS RESPONSES DURING TRIANGULAR WAVEFORMS OF ANGULAR VELOCITY ABOUT THE Y AND Z AXES

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Abstract Nystagmus slow phase velocity was measured during rotation stimuli consisting of short (12 sec) triangular waveforms of angular velocity. In one test series the horizontal semicircular canals were stimulated and in another test series the vertical canals were stimulated. The data were fit by equations derived from the assumption that the responses depend upon a cupula-endolymph system that responds like an overcritically damped torsion pendulum. Mean long time constant (Π/Δ) values found for the horizontal and vertical canal responses were, respectively 16 sec and 7 sec, consistent with previous findings, whereas gain constants found for the horizontal and vertical canals were, respectively 8.0 sec and 5.4 sec. Procedures for quickly extracting these parametric values from nystagmus records are described and, for practical reasons, the effects of stimulus distortion on the estimates of parameters were also considered

In previous reports parameters of the subjective reaction to semicircular canal stimulation were estimated from responses to a series of test stimuli consisting of short triangular waveforms of angular velocity (Guedry et al., 1971 *a*, 1971 *b*; Owens & Guedry 1969). This method appears to offer some practical advantages in regard to reliability and ease of measurement of vestibular sensation. The feasibility of using similar test procedures, as outlined by Guedry et al. (1971 *b*) in order to permit estimation of nystagmus response parameters is examined in this report. Both horizontal and vertical canal responses were evaluated and compared to determine whether or not the method is sufficiently sensitive to detect known differences in responses from the two sets of canals.

These procedures are based on a set of equations, derived from the torsion pendulum model which has been used extensively by van Egmond et al. (1949). The equations assume an ideal stimulus waveform, but in practice the waveform is often distorted due to performance limitations of rotary devices. Minor deviations from the ideal waveform are probably inconsequential, but the resulting errors may become significant when, for example fine discriminations between individuals are made or when measurements from several laboratories are compared. Therefore the effect of stimulus waveform distortion on parameter estimation was also examined in this report.

PROCEDURE

Subjects

Twenty US naval and marine officers served as subjects. These men ranged in age from 20 to 26 years. All had recently passed standard Navy flight physical examinations without signs of vestibular disorders.

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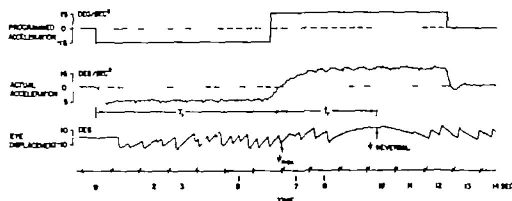


Fig. 1. A sample record showing programmed acceleration, actual acceleration, and recorded eye displacement for stimulation of the vertical semicircular canals. Peak slow phase eye velocity ($\dot{\psi}_{max}$) is measured approximately at the end of the acceleration period (T_1), and the time interval (t) is measured from the end of T_1 to the point of response ($\dot{\psi}$) reversal.

Apparatus

The rotation device was a Stille Werner RS-3 rotator fitted with a rectangular platform and a removable chair. The device was controlled by an external command voltage generated by a low frequency waveform generator. Stimulus angular acceleration was recorded from an accelerometer mounted on the rotation platform, and angular velocity was recorded from a tachometer attached to the drive motor.

Appropriately placed Beckman electrodes were used to record corneoretinal potentials from the subjects. These potentials were led through sliprings to a Sanborn 350 recording system and displayed on a chart recorder. The time constant of the amplification system was 2.5 sec.

Stimulus angular acceleration and velocity were also recorded on the chart display and angular acceleration was recorded on magnetic tape. The angular acceleration signal was later fed into an analog computer to generate a theoretical response curve for comparison with the one obtained from the prediction equations.

Method

Responses from both the horizontal and vertical semicircular canals were tested. To stimulate the horizontal canals, the subject was seated upright in the chair so that his z-axis was aligned with the axis of rotation. To stimulate the vertical canals, the chair was removed and the subject was positioned on his right side on the platform so that his y-axis was aligned with the axis of rotation. Half of the subjects were tested in the seated position first and half were tested in the right-side down position first.

The stimulus consisted of a triangular waveform of angular velocity formed by programming a 15 deg/sec² acceleration to last for 6 sec, followed immediately by deceleration of the same magnitude and the same duration. This stimulus was administered ten times in each position with the direction of rotation alternated from trial to trial.

Subjects were tested in total darkness with their eyes open. Mental alertness was maintained by requiring the subjects to add a series of numbers read to them during stimulation and to answer after stimulation had ceased. Eye movements were calibrated before and after each stimulus presentation. The inter-trial interval was 30 sec.

The nystagmus records were scored with a device (Guedry & Turnipseed, 1967) that provides readout, in both graphical and digital form, of slow phase eye velocity as a function of time. In addition, two measurements were obtained for calculation of parameter estimates. The first measure was the magnitude

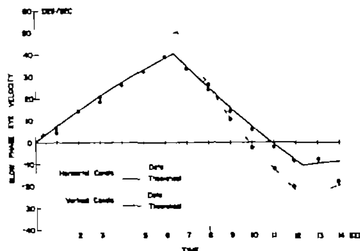


Fig. 2. Nystagmus responses from stimulation of the horizontal and the vertical semicircular canals by a triangular waveform of angular velocity. Data points represent the mean of twenty subjects × ten trials. Smooth curves represent theoretical responses calculated from the prediction equations.

of peak slow phase eye velocity ($\dot{\gamma}_{max}$) and the second was the time interval (t_r) from the end of the acceleration period (T_1) to response reversal. Fig. 1 illustrates the way in which these two measures were obtained.

Calculations of parameter estimates were based on the assumption that the vestibular stimulus was a triangular waveform of angular velocity formed by a constant acceleration followed immediately by a constant deceleration of the same magnitude and duration. However, the actual stimulus waveform was distorted, as shown in Fig. 1, particularly when the angular acceleration reversed direction. As a result, acceleration persisted beyond the point of initial change. Thus, for parameter estimation, the point at which acceleration passed through zero was chosen to mark the end of T_1, the beginning of t_r, and approximately when $\dot{\gamma}_{max}$ should occur.

Two theoretical response curves of slow phase velocity were generated, one from the prediction equations (Guedry et al., 1971 *a*) assuming an idealized acceleration waveform, and the other using the actual acceleration waveform recorded on magnetic tape as an input to an analog computer programmed with the appropriate second-order differential equation. The latter response curve was obtained by manipulating the values of the program to approximate as closely as possible the measured slow phase eye velocity as a function of time. Both curves were then compared in order to assess the effects of stimulus wave form distortion.

RESULTS AND DISCUSSION

Estimation of response parameters

Mean nystagmus responses for the group are shown in Fig. 2. Significant differences were found between the responses of the horizontal canals (z-axis rotation) and those of the vertical canals (y-axis rotation). The total slow phase displacement of the two responses was approximately the same, but the peak magnitudes of both acceleratory and deceleratory nystagmus were greater and the reversal occurred sooner for the vertical canal response. These differences were statistically significant ($p < 0.0005$).

According to the equations derived in previous reports (Guedry et al., 1971 *a*, 1971 *b*), the nystagmus response can be specified if the values of two parameters, Π/Δ and $K_e(\theta/\Delta)$, are known. The value of Π/Δ can be determined from t_r, and once Π/Δ is known, the value of $K(\theta/\Delta)$ can be determined from $\dot{\gamma}_{max}$. In practice, it is somewhat tedious to calculate these values from the equations. Therefore nomograms were prepared, and are shown in Figs. 3 and 4. The use of these nomo-

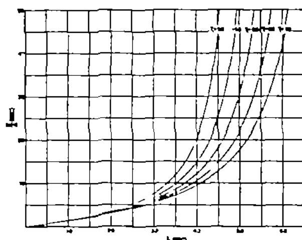


Fig. 3. Relationship between t and Π/Δ

grams is illustrated with the average values of t and $\dot{\psi}_{max}$ found in this study. For the horizontal canal response t was 4.5 sec and T_1 was 6.4 sec. Thus, the value of Π/Δ interpolated from Fig. 3 is about 16.0 sec. $K(\theta/\Delta)$ can be estimated from Fig. 4 by locating the intersection of a 6.4 sec T_1 curve with the Π/Δ value of 16 sec to obtain the $K(\theta/\Delta)/\dot{\psi}_{max}$ value of 0.2 sec^2/deg. When this is multiplied by the mean $\dot{\psi}_{max}$ values of 40.2 deg/sec, a $K_s(\theta/\Delta)$ value of 8.0 sec is obtained.

For the vertical canal response, t was 3.3 and T_1 was 6.6 sec; therefore, Π/Δ is 7.0. A value of $K(\theta/\Delta)/\dot{\psi}_{max}$ of 0.11 sec^2/deg was then obtained from Fig. 4 which, when

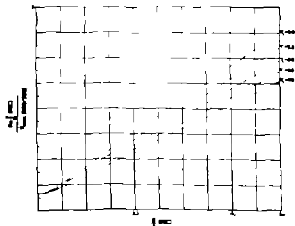


Fig. 4. Relationship between Π/Δ and $K(\theta/\Delta)/\dot{\psi}_{max}$ for an angular acceleration of 15 deg/sec²

multiplied by the $\dot{\psi}_{max}$ of 49.1 deg/sec, yields $K_s(\theta/\Delta)$ of 5.4 sec.

In the same way, parametric values can be obtained for other nystagmus data, once t and $\dot{\psi}_{max}$ have been measured. The nomograms were calculated for acceleration durations (T_1) of 5 to 7 sec. Pilot studies indicated that this range is of practical value when angular acceleration is 15 deg/sec² since the nystagmus response is difficult to score if the duration of acceleration is much less than 5 sec, and the errors introduced by response adaptation (Young & Oman, 1969) may become large if acceleration lasts much longer than 7 sec.

The Π/Δ determinations from Fig. 3 are independent of the magnitude of acceleration, but the $K(\theta/\Delta)$ values can be obtained from Fig. 4 only for an acceleration rate of 15 deg/sec². For other acceleration rates, the correct $K(\theta/\Delta)$ value can be calculated from Fig. 4 if the value of $K(\theta/\Delta)$ found from the figure is multiplied by 15 deg/sec² and then divided by the acceleration rate actually used.

The estimates obtained here for Π/Δ are generally consistent with those found by other investigators using various methods (Benson & Guedry, 1971; Guedry et al., 1971 a; Melvill Jones et al., 1964) thus supporting the validity of this procedure. Accurate estimates of $K_s(\theta/\Delta)$ have heretofore not been readily available, although calculation from data of Collins & Guedry (1967) collected during prolonged angular acceleration resulted in similar values. *Further support for this procedure comes from* the close fit to the data of the theoretical response curves generated by the prediction equation. Fig. 2 shows that the equation accurately predicts the horizontal canal responses and for the most part, vertical canal responses. However, with vertical canal stimulation there is a fairly pronounced departure of the rise in response during the initial acceleration from the theoretical rise curve. This may be attributable to difficulties in recording and scoring vertical nystagmus (Benson & Guedry, 1971; Ford, 1959; Melvill Jones et al., 1964) but it may also be due to a real departure

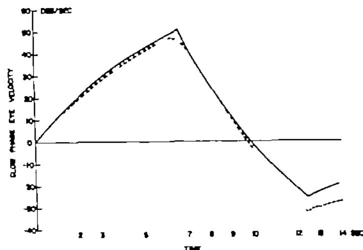


Fig. 5. Effect of stimulus waveform distortion during vertical canal stimulation. —— Theoretical response curve generated by the prediction equation assuming a perfect triangular waveform stimulus; ---- Theoretical response curve generated by an analog computer from the actual stimulus used in this study.

from the theoretical prediction. Nystagmus elicited by passive movement lacks the preparatory eyelid and brow movements which naturally accompany voluntary head rotations about the y-axis. The absence of these and other sensory data usually present in natural active movement may contribute to slow rise of the response, but, alternatively, the fact that the nystagmus velocity waveform approximates the shape of the stimulus velocity waveform more clearly than does its theoretical counterpart may reflect a need for restructuring some theoretical concepts.

Effects of stimulus waveform distortion

It was shown in Fig. 1 that the rotation device used here does not reproduce exactly the programmed stimulus waveform. Distortion was more severe during y-axis stimulation than during z-axis stimulation due to the greater rotational inertia that occurs when the subject's body is in the right-side-down position. Any amount of stimulus distortion is undesirable; nevertheless, it is a common problem with the rotary devices available in most vestibular laboratories, so an attempt was made to assess its effects on response prediction. In Fig. 5 the theoretical response curve obtained from the equation (assuming a perfect triangular stimulus waveform) is compared with the theoretical response curve generated on an analog computer using the actual distorted stimulus waveform recorded during vertical canal (y-axis) stimulation. This amount of distortion had little effect, as indicated by the similarity of the two response curves. It introduced some errors when estimating response parameters from the equations, but these were within an acceptable margin for most purposes. Using the actual stimulus waveform, Π/Δ was estimated to be 7.3 sec and $K_s(\theta/\Delta)$ was 6.5 sec, whereas using the programmed waveform, Π/Δ was 6.8 sec and $K_s(\theta/\Delta)$ was 5.4 sec.

Individual differences

Parametric values were calculated in this study from the averaged responses of a group of subjects, but the procedure is applicable as well to the evaluation of individual responses. Large differences were found among the 20 subjects in this sample: estimates of Π/Δ ranged from 9.9 to 32.7 sec for the horizontal canals and from 5.5 to 10.6 sec for the vertical canals, $K_s(\theta/\Delta)$ ranged from 4.9 to 11.2 sec for the horizontal and from 4.2 to 8.2 sec for the vertical canals.

These estimates appear to be reliable. From measures of intrasubject variability the 95% confidence interval for t was found to be ± 0.20 sec for the horizontal canals and ± 0.23 sec for the vertical canals. The 95% confidence interval for v_{max} was ± 5.68 deg/sec for the

horizontal canals and ± 8.05 deg/sec for the vertical canals. These confidence intervals were achieved from averages based on 10 trials. Greater precision could be gained by using averages over more than 10 trials, but the test procedure would be lengthened and its clinical potential usefulness diminished. Also a significant decrease in the t measure was noted with repeated presentations of the stimulus. This decrease was only 0.2 to 0.3 sec over the 10 trials, but it might have been larger and consequently more troublesome if more trials had been presented (Groen, 1957) It is unlikely that the decrease was due to a decline in alertness over trials because the other response measure, ψ_{max} was not significantly affected.

The present and the preceding reports (Guedry et al. 1971 *a* 1971 *b*; Owens & Guedry 1969) have described procedures for estimating parameters associated with both nystagmus and subjective responses to semicircular canal stimulation. These tests appear to be both reliable and relatively simple to administer and score.

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ZUSAMMENFASSUNG

Parameter der Nystagmusreaktion wurden mittels eines Testverfahrens abgeschätzt, das kurze, dreieckförmige Wellenformen der Winkelgeschwindigkeit benützte. Schätzungen des Mittelwertes wurden in folgender Weise bestimmt: Π Δ = 16.0 Sek und $k_m(\theta\ \Delta)$ = 8.0 Sek. für die horizontalen Bogengänge und Π/Δ = 7.0 Sek. und $k_m(\theta/\Delta)$ = 5 4 Sek. für die vertikalen Bogengänge. Die Π/Δ Werte stimmen mit denen anderer Methoden überein. Werte für $k_m(\theta\ \Delta)$ sind bisher nicht ermittelt worden. Bestimmung der Wirkungen von Reizverzerrung auf die Werte der Reaktionsparameter und Abschätzungen der inter und intrapersonalen Variabilität werden vorgelegt, ebenfalls Nomogramme, die eine einfache und genaue Methode für die Berechnung von Π/Δ und $k_m(\theta/\Delta)$ erlauben.

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MICROFILM STORING TECHNIQUE IN ELECTRONYSTAGMOGRAPHY

Two Years of Experience

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Abstract. At the Regional Hospital, Örebro, Sweden, an EEG routine was established 4 years ago including ADB and integrated microfilm technique. Two years ago the microfilm technique was also applied to the ENG routine, 3 M microfilm cards being used for storing records and typewritten data. Information is regained by means of a microfilm reader apparatus or a microfilm projector paper copies may also be made. The microfilm technique permits much easier and more rapid examination of previous records compared *with the original paper diagram evaluation. This is* important in the daily handling of the ENGs, especially when estimating possible progress or regression in the course of various vestibulary diseases. The microfilm method also has reduced storing space requirements to a minimum.

The storing of various documents concerning patients has become a great problem in hospitals. The archives increase at an accelerating speed. In Sweden an official committee has presented (1968) an analysis concerning the problem of medical archives (called "Arkiv inom hälso- och sjukvård") From this investigation a few examples may be mentioned. A 500-bed hospital is assumed to require 75 shelf metres a year for the storage of additional patient journals. The archives of an X-ray department with 50 000 investigations a year will increase by 143 shelf-metres. An EEG laboratory needs 12 shelf metres to store one year's production of 2 500 records; an ECG laboratory will fill up 25 shelf metres with 90 000 ECGs. One can only partly solve the problem by weeding out papers. Legal rules protect the different sorts of medical documents: one has to keep them in the archives for a varying number of years, the time being dependent on the type of document and country concerned.

The committee mentioned above has not proposed any outlines concerning ENGs but it seems natural to follow the same suggestions as for EEG records keeping them in the archives for 10 years. Because of the continuously increasing problem of archive enlargement one is forced, however to consider other solutions. Such a method is microfilm technique.

In the Department of Clinical Neurophysiology of the Regional Hospital in Örebro a microfilm method was established 4 years ago, the equipment since then being used in the daily EEG routine integrated with an ADB technique. From these 4 years the experiences are very encouraging, as stated by Sörbye (1972) The method involves microfilm photographing of all relevant information written in the referral card, the total report, selected parts of the record, calibration markings and the recording schemes. All this information is kept for the future in the small film square in a data card which also contains automatically punched information, such as the patient's name and other identification data, the latter

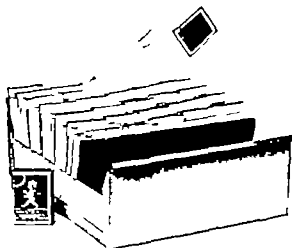


Fig 1 The archive box, containing about 1 000 microfilm cards. One microfilm square is seen.

to be read visually or by computer In this connection it should be mentioned that from the visually interpreted EEG record the computer is producing an automatically written report as well as storing the patient and EEG data on magnetic tape, the latter affording the possibility of later statistical investigations, etc. Concerning ENG records, the general handling f these up to now has varied from place to ace. In some hospitals the records are thrown way after the report has been written, in other clinics they are kept for some time Until 2 years ago the records of the Otoneurological Laboratory of the E.N T Clinic in Örebro were not archivated due to lack of archive space It was obvious, however that the information of the records could be valuable even after long time Therefore it was considered a good idea to try the microfilm technique which had already shown its great value in the EEG routine. With this method the main advantage would be the space saved in the archives. The margin of this area of the Otoneurological Laboratory was so small that even the actual production of 700 ENG records a year certainly was of importance After microfilm photography the total production of 3 years can be stored in an ordinary shoe box (Fig 1).

METHOD

During the past 2 years the following ENG microfilm routine has been used. A short case history and the result of the ENG investigation are photographed together with all the relevant parts of the records. The dry and fully mounted microfilm card comes out 45 seconds after a button being pushed on the microfilm camera the next record in the meantime being prepared for photography The identification data etc. are written at the top of the film card with an ordinary typewriter the card then being placed in the archive after a routine control of the data and the quality of the reproduction

The microfilm camera of the EEG laboratory has been used for photographing (3 M 2 000 from 3 M Company)

For retrieval of information from the microfilm card there are several possibilities:

1 *Microfilm reader apparatus*

The enlarged film square should be visible in total on the screen, to get the best survey of the records and the best basis for estimating asymmetries etc This is the case in the Normandale model 1518 (WST) where the screen measures 36 × 43 cm (0.16 m²) meaning a fourfold reduction of the original area which has been photographed. Another apparatus of the same type is "Caps" from Ingut Company

2. *Paper copies*

These can be produced in a reader-printer for instance Filmac 200 (3 M Company), giving an area of 61 × 45 cm (0.27 m²), which means about half the original area.

3 *Microfilm projector*

A projector specially constructed for microfilm cards gives good sharpness up to the picture size of at least 4 × 6 m. This opens up

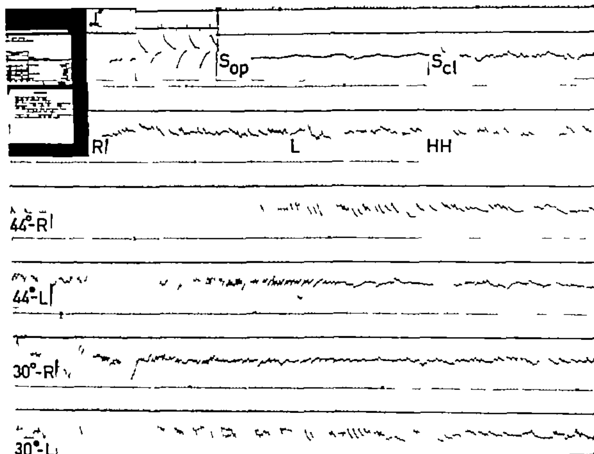


Fig. 2. Enlarged microfilm square. ENG. With closed eyes (S.) spontaneous nystagmus to the right is seen. In the right, left and hanging head positions (R, L and HH) there is also a nystagmus to the right. In the caloric tests a slight symmetrical preponderance to the right is observed. (Woman, 41, with a 6 month history of rotary vertigo attacks.)

possibilities for demonstration of ENG records even for larger groups.

Using the greatest reducing factor of the camera (24 ×) the area at disposal for photography is 91 × 68 cm, i.e. 0.62 m². A small part of this area is used for the patient identification data, the concentrated case history and a short report of the result of the ENG investigation (typewritten so far). Disregarding the upper left corner containing this information (Fig. 2) the area to be occupied by the ENG record still exceeds 0.5 m². In this area a more than 5 metres strip of paper measuring 12 cm across may be photographed. With such a paper from an Elema Schönander "Mingograph 81" a 2-channel registration of horizontal nystagmus will be suitable, one with short and one with long time constant. Moreover one may add 2 further channels, for instance for vertical nystagmus and vestibulospinal reflex.

We want to stress the importance of marking the different parts of the ENG carefully before microphotography. This can be done by means of large rubber stamps for each relevant part of the record (concerning the marking letters, see within parentheses after the different head positions stated below).

As shown in Fig. 2, a representative strip of paper has as a rule been microphotographed from each of the following registrations (when nothing else is stated the patient is lying supine with a 30 degree flexion of the neck. S)-

1. Calibration. With eyes starting from zero position a 5 degree "horizontal" deviation to each side has on the paper as a rule been given a total amplitude of 10 mm (CAL).

2. Patient looking at a point 30 degrees "horizontally" deviating from the zero position, right and left alternatively.

3. Patient fixating a point on the ceiling at zero position (S, op).

4. Same, but eyes closed (S, cl).

5. Head turned to the right, eyes closed (R).

6. Head turned to the left, eyes closed (L).

7. Head hanging down, eyes closed (HH).

8–11. Four registrations of the caloric reactions from stimulating right and left ear with water of 44 and 30 degrees (44 —R, etc.) stimulation time being 40 sec with a constant water flow (Ototerm from Kifa).

In the microfilm square, parts 1–7 of the registration will take two of the six possible horizontal strips, the last four being left for the caloric tests, one for each of parts 8–11. When photographing these 4 registrations their corresponding points of water flow ending should be placed on the same vertical line. Hereby one has the great advantage of easy comparison of the results concerning duration, amplitude, frequency and speed of the slow phase. This is important, the main interpretation of the caloric reactions being based on a comparison between these single parameters.

DISCUSSION

In many vestibular diseases, e.g. vestibular neuronitis, streptomycin and dihydrostreptomycin lesions, Ménière's disease and suspected acoustic neurinomas, it is important following up a series of ENGs over a long period of time. For interpreting possible progress or regression in a certain patient it is certainly valuable to be able to examine the previous records themselves and not only the descriptions. Also when consecutive reports record a shift in the direction of nystagmus it is valuable to have the records kept for control concerning possible mistakes.

Microfilm technique not only offers the possibility of keeping a large number of records in a small archive unit, it also permits examination of the registrations in a shorter time and with a better total view of eventual changes than before. The unfolding and arranging of previous ENG papers is no longer necessary. Paper copies of the microfilm square may follow the patient when being referred to another clinic. Such copies may also be added to the report to the referring colleagues. This has proved to increase their interest in the investigation and to widen their understanding of the interpretation. Projection permits easier demonstration for larger groups, especially when discussing details in a series of investigations.

The method described represents new possibilities for the handling of ENG information in an easier way. At the same time the archive problems are solved. In short, the microfilm technique has proved to save space, time and trouble.

RÉSUMÉ

A l'Hôpital Régional d'Orebro (Suède) on faisait depuis quatre ans des EEG de routine. On en tirait un microfilm et confiait à un ordinateur (ADB) les enregistrements. Depuis deux ans le microfilm a été utilisé de la même façon pour les Electro-nystagmogrammes. On a employé des cartes de microfilm (3 M) pour les diagrammes et les informations écrites. L'examen du microfilm peut être fait au moyen d'un lecteur ou d'un projecteur de microfilms — ou on peut en faire une photocopie. L'examen d'un ENG ainsi traité prend moins de temps que la lecture d'un document original et la comparaison entre plusieurs ENG est aussi plus facile à faire, ce qui est important, puis qu'on a souvent besoin de comparer une série d'ENG pratiqués à différents stades de la maladie pour estimer l'évolution de différentes troubles vestibulaires. Le microfilm a aussi l'avantage de réduire l'espace de rangements au minimum.

ZUSAMMENFASSUNG

Seit vier Jahren werden im Landeskrankenhaus in Örebro, Schweden, die Elektroencephalogramme routinemäßig auf Mikrofilm gelagert und die Resultate durch integriertes ADB-Verfahren geliefert. Seit zwei Jahren haben wir die Mikrofilmmethode auch für Elektronystagmogramme (ENG) verwendet. Es werden 3 M Mikrofilmkarten für die Lagerung der Diagramme

und maschinengeschriebene Daten verwendet und zum Lesen dieser Karten Mikrofilm-Leseapparat, Mikrofilm-Projektor oder auch Papierabzüge. Die Mikrofilmmethode erlaubt behändigere und schnellere Untersuchung früherer Aufnahmen im Vergleich mit dem Studium von Originaldiagrammen, was von Bedeutung in der täglichen Arbeit mit ENG ist, wo man oft eine Folge von Diagrammen untersuchen will, um einen eventuellen Progreß oder Regreß im Verlauf von Krankheiten im Vestibularissystem aufzudecken. Die Mikrofilmmethode hat den Bedarf an Lagerraum auf ein Minimum herabgebracht und ermöglicht Demonstration von Diagrammen an der Wand mit einem Projektor.

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TEMPORAL INTEGRATION OF ACOUSTIC ENERGY IN PATIENTS WITH PRESBYACUSIS

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Abstract The ability to integrate acoustic energy over time, i.e. temporal integration, can be measured by short tone audiometry Abnormal temporal integration has been considered as one of the reasons for reduced discrimination in hearing impaired ears. The results of short tone audiometry in 46 persons with presbyacusis are reported. The frequencies 500 Hz, 1 000 Hz, 4 000 Hz, and 8 000 Hz are investigated. The results show that the ability to integrate acoustic energy over time in patients with presbyacusis is reduced compared to normals. It was possible to demonstrate quantitatively a relationship between the amount of hearing loss and th. temporal integration. The difficulties in discrimination for patients with sensory-neural hearing loss may to some extent be explained from the reduced mporal integration.

ɪenever a quantitative estimate of hearing oss is required, a standard pure tone audiometry based on tone pulses of 500 ms or more is performed. The spoken language contains many short and complex sounds thus the ability to hear these short sounds must also be of audiological interest.

The perception of short tones or temporal integration of acoustic energy can be measured by threshold determination of tone impulses of varying duration, i.e. short tone audiometry Abnormal temporal integration has been considered as one of the reasons for reduced discrimination in hearing impaired ears (Hinchcliffe 1970· Broadbent & Stephens, 1970), but little information in this topic is available This paper reports our results of short tone audiometry in 46 persons with presbyacusis.

MATERIAL AND METHODS

This investigation is based on patients, age 53 to 86, with the diagnosis presbyacusis and were selected among the patients in the ENT department and the Audiological Clinic, Gentofte Hospital.

The diagnosis was ensured by a typical history and otological and audiometric investigations. Subjects participating in this trial represent cases with mild as well as severe hearing losses.

Audiological equipment and testing procedure was the same as used in a previous study on normals (Pedersen & Elberling, 1972). The investigation is a monaural threshold determination using pure tone impulses of the frequencies 500 Hz, 1 000 Hz, 4 000 Hz and 8 000 Hz.

Equivalent energy time for stimulation was varied from about 2 ms to 1 000 ms. Prior to the investigation the subjects are informed about the nature of the test. Using the pure tone audiogram each threshold determination starts at a sensation level of 10 to 15 dB and the intensity is lowered in 2.5 dB steps.

At each frequency 10 different threshold measurements are performed corresponding to the 10 different impulse durations used.

Fig. 1 illustrates our method of calculating an estimate of the temporal integration (Pe-

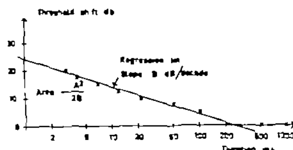


Fig. 1. Record from a test person. The measured thresholds at 1 000 Hz, for 10 different stimulus durations. The figure illustrates our method to calculate the relevant expressions A, B and $-A^2/2B$ for the temporal integration.

dersen & Elberling, 1972). In short the procedure is the following: the measured thresholds are plotted in a double logarithmic co-ordinate system, where the abscissa is the equivalent energy time of the stimulus, and the ordinate is the measured threshold shift in dB relative to the threshold for long stimulus (Bentzen, 1953). Using the method of least squares a regression line is calculated through the measured points. This line has a slope of B dB/decade and cuts the ordinate axis in the A dB

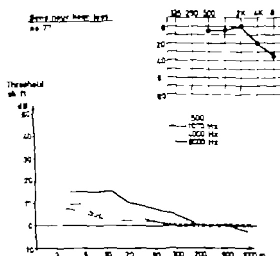


Fig. 2. The temporal integration in a case of mild presbyacusis with high tone loss. The temporal integration ($-A^2/2B$) at 500 Hz and 1 000 Hz are 32 and 27, i.e. normal. At 4 000 Hz and 8 000 Hz the temporal integration are 13 and 9, which is a significant reduction.

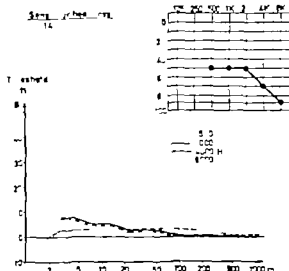


Fig. 3. The temporal integration of a severe case of presbyacusis. The temporal integration at the frequencies 500 Hz, 1 000 Hz, 4 000 Hz and 8 000 Hz are 18, 10, 10 and 0 respectively, calculated by the formula $-A^2/2B$. This value is significantly lower than in normal persons.

point. The area of the triangle formed by the abscissa axis, the ordinate axis, and the regression line is calculated and used as a quantitative measure of the temporal integration. The area can be calculated with the knowledge of the A- and B-value using the formula $-A^2/2B$.

RESULTS

Typical results from two subjects, a mild and a severe case of presbyacusis, are shown in Figs. 2 and 3.

The results of the A-value, the B-value and the area $-A^2/2B$ were correlated to the actual hearing loss for each subject and each frequency. From Fig. 4 it is seen that the A value (threshold shift) is decreasing, when the hearing loss increases.

From Fig. 5 it is seen that the numeric value of B (slope of the regression line) is decreasing, when the hearing loss increases. The temporal integration expressed as $-A^2/2B$ decreases, when the hearing loss increases. This is illustrated for each frequency in Fig. 6.

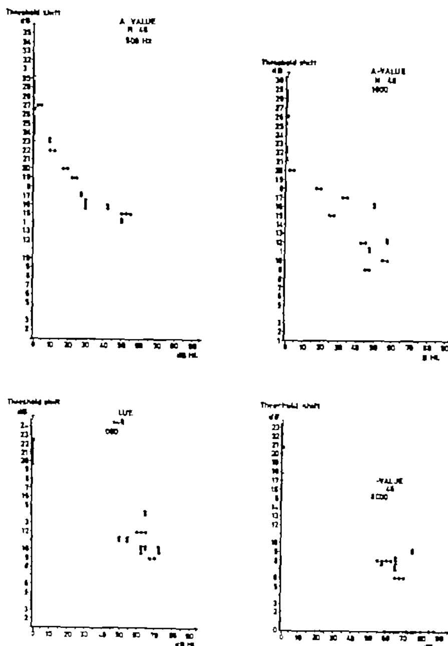


Fig 4 The individual A values (threshold-shift) versus the corresponding hearing losses at the 4 frequencies investigated. Mean values and standard deviations for normals are indicated

DISCUSSION

In short tone audiometry on pathological ears Miskolczy-Fodor (1953) investigated 30 ears with perceptive deafness and recruitment He demonstrated a decreased threshold shift for short tones in these patients compared with normals.

Harris et al. (1958) presented in a group of 25 patients, 10 cases of hearing defect due to cochlear lesions. In most of these patients abnormal temporal integration was observed.

Elliot (1963) gives the first description of a connection between hearing loss and the degree of change in temporal integration based on a study of 36 patients with sensory-neural hearing loss.

Watson & Gengel (1969) and Gengel & Watson (1971) reported 11 cases of hearing impairment due to cochlear defects. In these pa-

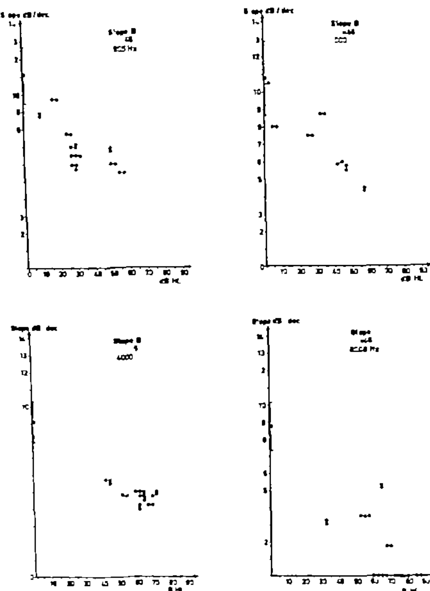


Fig 5 The B-values (slope of regression line) versus the corresponding hearing losses at the 4 frequencies investigated. Mean values and standard deviations for normals are indicated.

tients they found a reduced ability of the auditory system to integrate over time the acoustic energy in brief sounds.

Sanders & Honig (1967) concluded on basis of results from 14 patients that ears with cochlear pathology is clearly distinguished from normal ears by short tone audiometry

As a result of the investigations of Wright (1968) and Wright & Canella (1969) it is concluded that in patients with mixed conductive sensory-neural component contributes to the hange in temporal integration.

Most of the 46 persons with presbyacusis investigated needed Hearing Aid (HA) and consulted the audiological clinic for this reason. To investigate patients with a minor degree of presbyacusis a small number with a mild high-tone loss only was also included in the material. Care has been taken to exclude diseases other than presbyacusis, but influence of acoustic trauma cannot be excluded completely

From Fig. 4 it can be seen that the threshold shift (A-value) decreases, when the hearing-loss increases. Fig. 5 shows that the slope

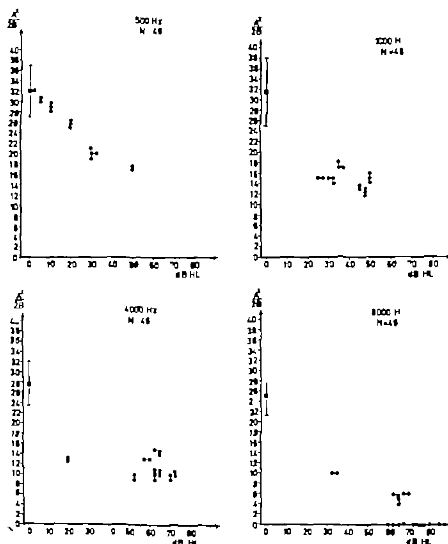


Fig 6 Temporal integration expressed as $-A/2B$, versus the corresponding hearing losses at the 4 frequencies investigated. Mean values and standard deviations for normals are indicated.

of the regression line is decreasing when the hearing loss increases. The temporal integra tion expressed by the value $-A^2/2B$ also shows a nearly inverse proportionality to the hearing loss as demonstrated in Fig. 6

Of the expressions A, B and $-A^2/2B$ we think that $-A^2/2B$ is the most relevant for the temporal integration.

The dots indicating B-values show the great est spread (Fig 5) while the dots indicating values of A and $-A^2/2B$ appear with nearly identical spread (Figs. 4 6). Of these two ex pressions $-A^2/2B$ is preferable, because changes in the B-value also is taken into ac count.

The results of short tone audiometry at 4 different frequencies in patients with presby acusis show that temporal integration of acou tic energy is reduced compared with normals (Pedersen & Elberling 1972), in agreement with the earlier investigations. It was possible to demonstrate quantitatively a relationship be tween the amount of hearing loss and the ade quate expressions A, B and $-A^2/2B$ for tem poral integration.

Difficulties in discrimination in patients wi sensory-neural hearing loss have called for ne audiological investigations (Hinchcliffe, 197 Broadbent & Stephens, 1970) Our investig tions confirm that in patients with presbyacus changes in thresholds produced by long ar short acoustic stimuli are smaller than in pe

sons with normal hearing. If these patients are fitted with a HA, supposed to produce transcient distorsion (overshoot) changes in thresholds produced by long and short stimuli are perceived with an even smaller or negative difference. This might to some degree explain the difficulties in discrimination with sensory-neural hearing loss, even when supported with HA.

ZUSAMMENFASSUNG

Die Fähigkeit, akustische Energie über Zeit hin zu integrieren, d. h. die Temporalintegration, kann mit Kurztonaudiometrie untersucht werden. Veränderungen der Temporalintegration wurden als eine der Ursachen von Diskriminationsschwierigkeiten in schwerhörigen Ohren beobachtet. Die Ergebnisse einer Kurztonaudiometrie von 46 Presbyacusis-Patienten werden hier mitgeteilt. Vier verschiedene Frequenzen (500 Hz, 1 000 Hz, 4 000 Hz und 8 000 Hz) sind untersucht worden. Die Resultate zeigen, dass die Fähigkeit, akustische Energie zu integrieren, bei Presbyacusis-Patienten reduziert ist, wenn man mit Normalgehör vergleicht.

Es war moglich, einen quantitativen Zusammenhang zwischen dem Grad des Hörverlustes und der Temporalintegration zu zeigen. Es ist wahrscheinlich, dass die mangelnde Temporalintegration bei Altersschwerhörigkeit in gewissem Masse die Diskriminationsschwierigkeiten dieser Patienten verursacht.

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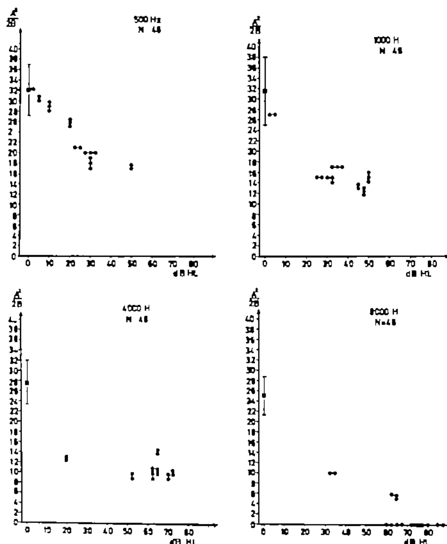


Fig 6 Temporal integration expressed as $-A^2/2B$, versus the corresponding hearing losses at the 4 frequencies investigated. Mean values and standard deviations for normals are indicated.

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The results of short tone audiometry at 4 different frequencies in patients with presbyacusis show that temporal integration of acoustic energy is reduced compared with normals (Pedersen & Elberling, 1972), in agreement with the earlier investigations. It was possible to demonstrate quantitatively a relationship between the amount of hearing loss and the adequate expressions A, B and $-A^2/2B$ for temporal integration.

Difficulties in discrimination in patients with sensory-neural hearing loss have called for new audiological investigations (Hinchcliffe, 1970, Broadbent & Stephens, 1970) Our investigations confirm that in patients with presbyacusis changes in thresholds produced by long and short acoustic stimuli are smaller than in per

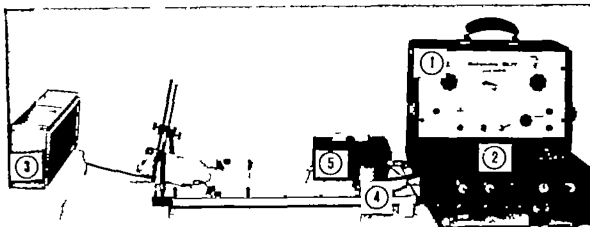


Fig. 1. Simplified equipment used for conditioning the guinea-pig to sound and for its Shiver-audiometry. *1* Audiometer. *2* amplifier. *3* loudspeaker (placed at exactly 20 cm from the animal's auricles); *4* sound switch; *5* tension regulator with switch for sending the electric shock through the electrodes (c) attached to the hind-paws of the guinea-pig.

the experimental auditory damage caused by us with various methods.

MATERIALS AND METHODS

The original article by Anderson & Wedenberg should be consulted for details, the following is a report on the fundamental data of simplified S.A.

The first simplification concerns the use, as a source of pure tones, instead of the more complex electro-physiological equipment, of a common audiometer (mod. 802/A or mod. 200, Amplifon Milan), connected to an amplifier-loudspeaker system of appropriate power. This complex, which must be calibrated before each experiment, produces pure tones of 125 to 8 000 Hz and of an intensity of −10 to +100 dB. It is used both to condition those animals which have already been subjected to a first selection and to carry Shiver-audiometry. Numerous preliminary experiments had allowed us to establish that the ideal experimental situation for us was to place the loudspeaker exactly 20 cm from the binaural axis of the guinea-pig, whose head—as in the original method—was held firm by a collar (Fig. 1).

A first examination of hearing based on the pinna reflex (acoustic reflex or Preyer reflex) makes it possible to ascertain the intensity which should be adopted for the various frequencies from 250 to 8 000 Hz tried out by us first for conditioning then for the audiometry.

Conditioning is obtained easily by means of the progressive presentation of pure tones at pre-determined intensities, each being followed at various intervals in order to avoid temporary conditioning, by a brief 2–5 V shock, applied through electrodes fixed to the animal's hind paws, by an appropriate tension regulator. During the conditioning phase, which takes place generally in 10–20 minute daily sessions, over a period of 3 to 8 days, a second selection of the animals takes place: so far they had been selected merely on the basis of general conditions of health and of the normality of the tympanic membrane or of their evident incapacity for one reason or another to learn. In actual fact, the guinea-pig is easy to condition and it is clear that its aptitude for learning increases as the conditioning session progress.

Another simplification introduced by us concerns the system for causing the shiver in the conditioned guinea-pig. Instead of the more or less complex systems of refrigeration—which are also, apart from anything else, a little noisy—we practise Shiver-audiometry in

a cold room intended for biochemical use thus the examination is conducted in the proper conditions of silence. Further advantages could derive from our present attempts to use a system similar to that of common cryostats. When placed in the cold room (0 –2 C), after 10 to 20 minutes the guinea-pig shows a clear shiver This, as well as its interruption by an appropiate acoustic stimulus and in conformity with Anderson & Wedenberg, can easily be recorded together with the sound stimulus by using a piezoelectric microphone connected to an ordinary two-channel cardiograph. How ever we prefer not to record the shiver just as we have abstained from any possible automation of the conditioning phase because we believe that it is very important that each phase of the technique be directly followed by the examiner

The values in dB of the minimum intensity which for the individual frequencies between 250 and 8 000 Hz, cause the interruption of the shiver correspond to the hearing threshold of the animal, and are marked on an ordinary human audiometric chart. In experiments on auditory pathology the initial normal values are set to zero and thus any pathological values can be appropriately corrected. On the chart we also always register the threshold values obtained for the same scale of frequencies with pinna reflex because as Anderson & Wedenberg have shown they are an indication of lesions to the receptor in other words of recruitment, if they remain more or less un changed when the S A reveals an auditory deficit.

Shiver-audiometry has been conducted both on albino guinea-pigs (Morini farm, R. Emilia, Italy) and on pigmented guinea-pigs of both sexes and of an age varying from 2 weeks to about 2 years. Normal auditory values have been obtained from guinea-pigs of about 45–60 days, corresponding to a body-weight of about 200–350 g. During a second phase cer tain guinea-pigs which, according to S.A. had normal hearing were used for pathological ex periments.

Four albino guinea-pigs were treated sub cutaneously four times a day with a dose of 250 mg per kg of body weight per day of sulphate kanamycin for 20 days. The be haviour of their hearing was studied every 5 days, at first in all 4 animals then after the interruption of the treatment, only in 3 of them one having died on the 19th day

In 4 albino and 4 pigmented guinea-pigs we studied auditory behaviour after an hour of hyperstimulation with a noise of a frequency band of 80 to 8 000 Hz, and of an intensity at the level of the guinea-pig s auricle and in our experimental conditions, equal to 126 dB (phonometer mod. 908, Amplifon, Milan) Shiver-audiometry was carried out after 4 hours, and 2, 6 and 8 days.

Finally in order to evaluate whether S.A could be used in experiments based on endo tympanic injection treatment, 4 guinea-pigs under ether narcosis were injected transtympanically with about 0.20 ml of a saturated sodium chloride solution in order to obtain a Ménière-like syndrome as described by Arslan (1969) Four other albino guinea-pigs of the same age acted as controls and were treated in the same manner with physiological solution. These were indispensable for as is well known, any liquid which is introduced into the guinea-pig s middle ear causes, on the one hand, the rapid disappearance of the pinna reflex and, on the other otitis. In an attempt to prevent otitis, the animals were treated with an intramuscular injection of 10 000 U O of sodium penicillin in 0 1 ml of distilled water at inter vals of 12 hours. S.A. was conducted on the 7th day

The data obtained from audiometric experiments have been elaborated statistically with an evaluation of the standard error of the aver age and an analysis of the variance.

RESULTS

Table I gives the average values and the standard deviation of the average obtained for the frequencies of 250 to 8 000 Hz in the audiomet-

Table I *Average auditory threshold* (± *E.S*) *expressed in dB for the frequencies of 250–8 000* Hz, *obtained by Shiver-audiometry in albino and pigmented guinea-pigs*

Guinea pig	No. of animals	250	500	1000	1 500	2 000	3 000	4 000	6 000	8 000 Hz
A. Albino	31	0.1 ±1.6	2.3 ±1.1	4.7 ±1.1	3.7 ±1.5	2.7 ±1.2	1.5 ±1.3	−1.7 ±1.4	−7.1 ±1.3	−3.9 ±0.7
B. Pigmented	5	25.0 ±1.5	28.0 ±1.2	28.0 ±3.0	28.4 ±2.6	33.0 ±2.0	29.4 ±1.7	28.0 ±4.5	20.8 ±1.6	28.0 ±2.0

A B $P < 0.001$ for all frequencies.

ric examination of 31 albino and 5 pigmented normal guinea-pigs in our experimental conditions.

In all the frequencies examined, a statistical comparison of the two groups has revealed a significant difference ($P < 0.001$) from which it may be deduced that in our experimental conditions the albino guinea-pig has a better auditory capacity than the pigmented one. The reason for this, for the time being, is a mystery to us.

Fig. 1 shows the average threshold curves obtained by S.A. from 20 albino guinea-pigs which, after all the usual checking operations, were considered to be normally-hearing, whereas in actual fact 4 of them had hypoacusia in almost all the frequencies examined. It

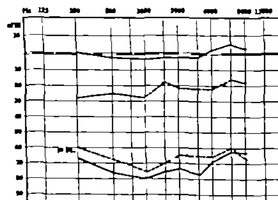


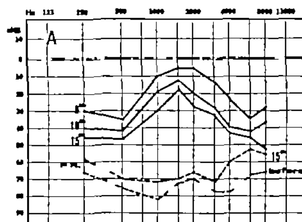
Fig. 2. Average curves of auditory threshold obtained with Shiver-audiometry in 16 albino normally-hearing guinea-pigs (——) and 4 albino guinea-pigs of the same group which, though apparently normal in preceding tests proved to have hypoacusia (–) P. R. average threshold curve obtained with the pinna reflex.

may be observed that this deficit was not revealed by the examination carried out with the pinna reflex. An anatomical examination of these animals showed that they were suffering mildly from unilateral or bilateral otitis. Shiver-audiometry therefore makes it possible to identify those guinea-pigs which really do have normal hearing, while any judgment as to normality which is based on general conditions of health, on the condition of the tympanic membranes and the presence of the pinna reflex could lead to erroneous selection.

Fig. 3 *a* and *b* show the behaviour of hearing during subcutaneous treatment with high doses of kanamycin. Since one of the guinea pigs died towards the end of the treatment, Fig. 3 *b* gives the average auditory curve of 3 animals only as obtained after the end of the treatment.

During the treatment we were able to detect a progressive auditory deficit, especially at high and low frequencies, while the 1 500 Hz frequency appeared to remain even. After suspension a recovery of the lower frequencies was detected, whereas the deficit of the higher frequencies persisted, and even the middle frequencies were involved.

The final result was a descending curve towards the high tones. The persistence of the pinna reflex during and after the kanamycin treatment indicates that the damage affects the receptors. Observations during the first phase of the experiment are curiously in harmony with the data of other authors who, by means of the cochleogram technique, have studied the neurosensorial lesion which can thus be pro-



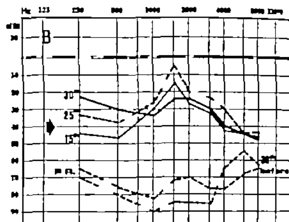
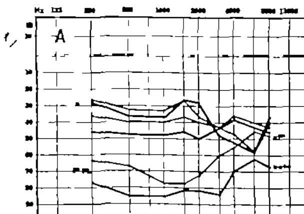


Fig 3 (*A*) Average hearing threshold curves in relation to the initial average values set to zero and obtained by Shiver-audiometry in 4 albino guinea-pigs during subcutaneous treatment with kanamycin (250 mg/kg of body weight/day) Examination shows a progressive auditory deficit for the frequencies of 500–1 000 Hz and 3 000–8 000 Hz. The behaviours of the pinna reflex (*P.R.*) indicates that lesion is in the receptors.

Fig 3 (*B*) After twentieth day (*arrow*) and suspension of the treatment, progressive recuperation may be observed in the 3 surviving animals for the lower frequencies, while the middle ones are involved and the higher ones continue to show a deficit.

voked (Ostyn & Tyberghein, 1968), whereas the deficit observed after the treatment is reminiscent of that to be met with in patients suffering from antibiotic intoxication.

Fig. 4 *a* and *b* refers to the audiometric results obtained with albino and pigmented guinea-pigs after acoustic hyperstimulation (white noise of 126 dB for an hour) From the average threshold curve obtained at various intervals from the trauma, it can be seen how immediately after it, the deficit is extremely important and almost equal for all the frequencies in the case of the albino guinea-pig, whereas it is more important in the medium frequencies in that of the pigmented animal. Moreover the behaviour of the pinna reflex during the experiment shows that here we have damaged receptors. But in the following phases of the



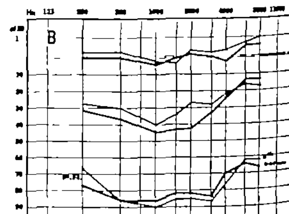


Fig 4 (*A B*) Evolution of the average auditory threshold curves (4 animals) obtained after 4 hours, 2, 6 8 days from an acoustic overstimulation (white noise 126 dB 1 hour) upon albino and pigmented guinea-pigs. (*A*) Albino guinea-pig. Compared with the normal average values set to zero, after a considerable initial deficit a progressive recovery may be observed for the 250–2 000 Hz frequencies and a further drop for the 3 000–6 000 Hz frequencies. The behaviour of the pinna reflex (*P.R.*) indicates a lesion of the receptors. (*B*) Pigmented guinea-pig. As early as the sixth day there is a complete recovery of the normal auditory functions.

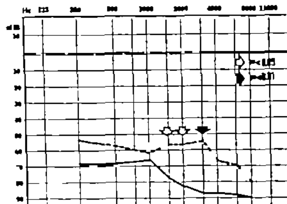


Fig. 5. Average curves of the hearing threshold, in relation to the normal values set to zero, obtained with Shiver-audiometry on the seventh day after the endotympanic injection of a saturated sodium chloride solution (——) and, respectively, of a physiological solution (- - -). The animals of the first group reveal a deficit for the 1 500–3 000 Hz frequencies.

experiment, the behaviour of hearing in the two experimental groups is entirely different. On the 8th day the albino guinea-pig showed a low degree of recuperation, limited to the low and medium frequencies while the deficit in the higher frequencies was more pronounced. The pigmented guinea-pig on the contrary revealed even on the 6th day a complete recuperation for all the frequencies examined.

This observation appears to be in agreement with other researchers (Galioto & Bonaccorsi, 1965) who had registered by a different method a weaker resistance of the albino guinea-pig's ear to the acoustic trauma, and thus appears to be a new proof in support of Cherubino's hypothesis (1968) that the pigment itself in conditions of hypoxia caused by the acoustic trauma, could well be a source of metabolic energy for functional recuperation. Such recuperation has been shown by present experiments to be only partial twenty days after the acoustic trauma as far as the albino guinea-pig is concerned.

Finally Fig. 5 shows the behaviour of the hearing of the albino guinea-pig 7 days after a bilateral endotympanic injection of a saturated sodium chloride solution. Comparisons were made with guinea-pigs treated with physiological solution. As statistic analysis has shown, there is an important deficit only for the frequencies between 1 500 and 3 000 Hz ($P < 0.05$ or 0.01). Since the endotympanic injection leads to the disappearance of the pinna reflex, we are not able to ascertain audiometrically whether it is a question of a deficit of the receptors, but the morphologic controls in our possession (unpublished data) show that as a result of endotympanic treatment with saturated sodium chloride solution there arises a serious alteration of the permeability of the membranous labyrinth, this being accompanied for the first hour by a general swelling of the dendrites of the internal hair cells. This lesion which is itself aspecific in that it has been met with in various experimental conditions (Spoendlin, 1970) proves that there is also sensori-neural damage. Moreover our audiometric results seem to agree with those obtained from cats under the same experimental conditions by means of other tests by Molinari (1971), who noted a deficit in the middle frequencies.

CONCLUSIONS

Since most of experimental otologic research is conducted on guinea-pigs, a technique which allows the majority of research workers to evaluate the behaviour of hearing in this animal in normal and in provoked pathological conditions can be important.

The simplification of the technique proposed by Anderson & Wedenberg as applied by us, furnishes a method which, in accordance with these authors' reports, fully corresponds to its purpose. Simplified S.A. is actually easy to practise insofar as it does not require complicated equipment but only common and easily obtainable instruments. Above all, compared with all other methods proposed so far it is the least expensive of tests and that which can be put to the most varied uses. The experiments given by us as examples show clearly how versatile it can be. It makes possible the identification of truly normally-hearing guinea

pigs, and indicates that in our experimental conditions the best animal for research work is the albino guinea-pig. Moreover it has made it possible to follow up in time the evolution of hearing in experiments of short and medium duration and given us indications, through the deficits observed as to the cochlear sectors which deserve morphological study. Also as experiments now being conducted have shown, the reconditioning of the animal might permit the prolongation of observation which at present lasts little more than 2 months, whereas it is possible to use this method on very young guinea-pigs whose audiogram could be obtained as early as their tenth day of life. The test based on the pinna reflex—which some investigators still use—has shown its inadequacy in evaluating the behaviour of hearing in the guinea-pig whereas Shiver-audiometry has been extremely useful in following up dynamically any possible auditory damage and in evaluating the difference in behaviour between the albino and the pigmented guinea-pig after acoustic hyperstimulation. Another advantage could be—when using the proper controls and statistic analysis—the possibility to study the effects caused by endotympanic treatment. We consider that these possible applications are well worth further study and are carrying this further at present. Certain pressing problems of otology can be dealt with more completely such as for instance the problem of identifying ototoxic drugs, this method having proved capable of establishing the extent and the seat of the damage: obviously this can be useful for precise evaluation in relationship to dosing, means of application, rhythm and duration of the ototoxic treatment. For all these reasons, Shiver-audiometry may be recommended as the simplest, most practical and least expensive of tests for the study of hearing in the guinea-pig this animal being the most extensively used in otological experimental research.

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ZUSAMMENFASSUNG

Der Hörversuch von Anderson und Wedenberg ist hier vereinfacht und wegen des Bestandteils, der seine Originalität bildet, Schauderaudiometrie genannt worden. Da seine Benutzung nun einfach und billig geworden ist, zeigt sich auch seine Vielseitigkeit, wie es die Versuche mit albinitischen und pigmentierten Meerschweinchen beweisen. Dank dieser Versuche konnte man Tiere mit Normalgehör identifizieren und dadurch feststellen, dass in unserem Versuchszusammenhang der Albino eine grössere Hörkraft als das pigmentierte Tier besitzt. Das Albino-Meerschweinchen weist auch eine grössere Verwundbarkeit der Ohrschnecke unter akustischer Hyperreizung auf. Die Schauderaudiometrie hat sich bei Versuchen von kurzer und mittlerer Dauer als ein wichtiger dynamischer Indikator der Gehörentwicklung erwiesen, da sie nicht nur die Entwicklung der Läsionen in der Zeit, sondern auch ihr Ausmass feststellt. Sie ist also sehr nützlich, da sie der morphologischen Forschung den Weg zu den am meisten verletzten Sektoren der Ohrschnecke zeigt, z.B. in Fällen von Kanamycinvergiftung oder nach akustischem Trauma oder nach lokaler Behandlung des Ohres mit einer gesättigten Chlornatriumlösung. Auf Grund dieser Eigenschaften bildet die Schauderaudiometrie eine wertvolle Vervollständigung der experimentellen otologischen Forschung.

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DER SUCCINATDEHYDROGENASE-NACHWEIS MIT HILFE DER PERFUSIONSTECHNIK AN DER COCHLEA DES MEERSCHWEIN CHENS UNTER NORMALBEDINGUNGEN UND NACH DAUERLÄRMEINWIRKUNG

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Abstrakt. Mit Hilfe der Perfusionstechnik wurde die SDH in der normalen Meerschweinchencochlea nachgewiesen. Abgesehen von dem Fehlen der Färbung in der Stria vascularis und in den Ganglienzellen des Ganglion spirale entspricht die Verteilung der Aktivität im wesentlichen den Ergebnissen bei der vielfach verwendeten Schnitt- und Stückinkubation. Nach 63 Stunden Einwirkung von 110 dB „weißem Rauschen (9 h Lärm, 15 h Pause, Samstag und Sonntag Pause) kommt es zu einem eindeutigen Abfall der SDH in den äußeren und inneren Haarzellen und den zugehörigen Nervenendigungen. Eine umschriebene Lokalisation des Aktivitätsabfalls auf ein bestimmtes Areal des Ductus cochlearis konnte nicht gesichert werden Die Ergebnisse werden diskutiert.

Entsprechend der hervorragenden Bedeutung der Succinatdehydrogenase (SDH) im Energiestoffwechsel der Zelle wurden im Rahmen der histochemischen Untersuchung des Innenohres häufig Arbeiten über ihre Verteilung in der Cochlea publiziert. Zahlreichen licht und elektronenmikroskopischen Studien nach Stück und Schnittinkubation (Vosteen 1956 *a b c* 1960 1961 Koide et al., 1962 Nakai, 1965 Nakai & Hilding, 1968) stehen relativ wenige Beobachtungen nach Perfusionsinkubation gegenüber (Gehrhardt, 1961 *a b* Schätzle & Misebeck, 1962, Spoendlin & Balogh, 1963 *a b* 1964).

Unterstützt durch einen Forschungsauftrag des Ministeriums für Gesundheitswesen der DDR.

Da nach unserer Meinung der Perfusionstechnik bei Untersuchungen des Cortischen Organs eine größere Bedeutung zukommt, als ihr momentan zuerkannt wird, fühlen wir uns berechtigt, unsere Ergebnisse, die im Rahmen methodischer Vorarbeiten zu Studien und Veränderungen nach Lärmbelastung durchgeführt wurden, zu publizieren.

MATERIAL AND METHODE

Insgesamt wurden 18 Meerschweinchen (250–500 g Gewicht) beiderlei Geschlechts mit normalem Preyer Reflex untersucht. In Urethan-Äther-Narkose erfolgte die Präparation und Eröffnung der Bulla tympanica sowie die Freilegung des runden und ovalen Fensters. Nach Anlegen eines apicalen Bohrloches in der Schnecke wurde ein PVC Schlauch in das runde Fenster eingekittet und das Inkubationsgemisch perfundiert.

Der SDH-Nachweis erfolgte mit dem Medium von Ogawa & Barnett (1965) mit TNBT als Indikator bei einer Temperatur von 60 Min. Sofort nach der Inkubation wurde mit neutralem, eisgekühltem, 4%igem Formalin mit einem Zusatz von 7,5% Sucrose (Geyer 1969) 10 Min lang per perfusionem vorfixiert.

Nach Dekapitation und Isolierung der Cochlea aus dem Felsenbein erfolgte im gleichen Medium die Nachfixierung 16 h lang bei 4 C

Die Entkalkung wurde in neutraler gesättigter Dinatrium EDTA Lösung (mod. n. Balogh, 1965) die durch eingeleitete Luftblasen ständig bewegt wurde, 7 Tage lang bei 20 C durchgeführt. Danach wurde in Polyäthylenglycol 600 nach Halbhuber & Geyer (1966) eingebettet, am Gefriermikrotom etwa 15 μm dick geschnitten und in Glyceringelatine eingedeckt. Als Kontrollversuche inkubierten wir nach Geyer (1969)

— unter Weglassen des Substrats
— nach Praeinkubation mit 4% Formalin, 30 Min bei 20 C
— substratfrei nach 30 Min. Auswaschen des endogenen Substrats mit 0 44 M Sucroselösung
— *unter Zusatz von 1,5 ml 0 1 M Natrium* malonat zum Inkubationsmedium.

Die Beschallung von insgesamt 6 Tieren erfolgte nach Dieroff (1971) sowie Dieroff & Beck (1966) durch Einwirkung von „weißem Rauschen" mit einer Intensität von etwa 110 dB 63 h lang (9 h tägl., 5 Tage hintereinander Samstag und Sonntag Pause, danach nochmals 2 Tage lang) 15 h nach der letzten Beschallung wurde die histochemische Untersuchung begonnen

ERGEBNISSE

Normales Cortisches Organ

Im normalen Cortischen Organ wurden die stärksten SDH-Aktivitäten in den inneren und äußeren Haarzellen nachgewiesen (Abb 1 *a*) wobei die Formazanablagerungen in den inneren Haarzellen stets intensiver schienen.

Die Farbniederschläge in den äußeren Haarzellen waren in der Intensität abgestuft (Abb 1 *b*) wobei ein kräftiges Depot in der Intermediärzone (Schema nach Iurato 1961) von einem infranukleären, noch intensiveren Formazanlager zu unterscheiden war Im Bereich der perinukleären Zone fand sich eine deutliche farbliche Betonung der zellwandnahen Bezirke und gegenüber den erwähnten Depots in der Intensität abfallende im übrigen Cytoplasma unter Aussparung des Kerns verteilte Farbablagerungen. Die inneren Haarzellen (Abb 1 *c*) zeigten eine derartig deutliche Abstufung in der Färbung nicht. Die Farbniederschläge waren granulär sie lagen relativ gleichmäßig verteilt unter Aussparung des Kerns *im gesamten Cytoplasma. Nur bei gelegentlich* etwas schwächerer Gesamtfärbung fanden sich deutlichere Depots in der intermediären Zone und dem infranukleären Bereich

In der Zone der Nervenendigungen am unteren Zellpol der äußeren Haarzellen (Abb. 1 *a* 2) wurden kräftige Ablagerungen von Farbstoff gefunden, die von den kappenförmigen infranukleären Depots deutlich abgrenzbar und auch weniger intensiv waren. Von diesem Bereich zogen sich entlang der Randbezirke der Deiters-Zellen in Richtung Basilarmembran kleinere, perlschnurartig aneinander gereihte Farbstoffpunkte (Abb 2) Es konnte auch bei maximaler Vergrößerung nicht sicher zwischen extrazellulärer und intrazellulärer Lage *entschieden werden*. Bei Darstellung des Tunnelspiralbündels (Abb. 1 *a* 1 *c*) im Schnitt wurde es bei genügender Vergrößerung immer deutlich angefärbt gefunden. Gelegentlich war auch die Tunnelfaser positiv

Die Zone der Nervenendigungen unter den inneren Haarzellen (Abb 1 *a*, 1 *c*) zeigte ebenfalls intensive SDH Aktivitäten, wobei die Formazandepots deutlich kelchartig den unteren Zellpol *bis in Höhe des Zellkerns hinauf* umgriffen. Von dort zogen sich die Farbstoffablagerungen *(Abb 1 a, 1 c) kontinuierlich* in gleicher Stärke bis zur Habenula perforata hin. Modioluswärts setzten sie sich dann unter regelmäßigem und stetigem Intensitätsabfall entlang der Nervenfasern fort. Weiter zur Nähe des Ganglion spirale hin konnten noch immer vereinzelte Ansammlungen von Formazangranula im Verlauf der Nervenfasern nach-



Abb 1 SDH-Reaktion am normalen Corti-Organ des Meerschweinchens. (*a*) Massive Reaktion in äußeren und inneren Haarzellen, jeweils eingeschlossen die Zone der Nervenendigungen. Besonders zu beachten das positive Tunnelspiralbündel (Tsp). 600 (*b*) Äußere Haarzellen mit typischer Verteilung der Formazandepots. 1 500. (*c*) Innere Haarzellen, kelchartige Darstellung der Zone der Nervenendigungen. Anfärbung der Nervenfasern. positives Tunnelspiralbündel. × 1 500.

gewiesen werden. Selbst im intraganglionären Spiralbündel wurden sie gelegentlich gefunden.

Die Nervenzellen des Ganglion spirale blieben eindeutig negativ

Im Zellkörper der Deiters-Zellen, abgesehen von den beschriebenen randständigen perlschnurartigen Farbstoffdepots, wie auch in den übrigen Stützzellen des Cortischen Organs



Abb 2 SDH Reaktion im Stützellbereich unter den äußeren Haarzellen. Positive Nervenendigungen, Anfärbung der äußeren Spiralfasern, Deiterszellen negativ 1 500.

und in den Boettcher Zellen konnten keine Aktivitäten nachgewiesen werden.

Mehr oder weniger vereinzelt und unregelmäßig verteilt wurden SDH Aktivitäten in den Interdentalzellen gefunden (Abb 3 *a* 3 *b*) die



Abb 3 SDH Reaktion an den Interdentalzellen der normalen Meerschweinchencochlea. (*a*) 4 positive Interdentalzellen zwischen mehreren negativen. 610 (*b*) Deutliche Reaktion im gesamten Phalanxbereich bei fehlender Färbung, im vacuolaren Hohlraumbereich. 1 440.

wenn positiv recht kräftige Farbstoffablagerungen zeigten Dabei ließen sich immer im gesamten cytoplasmahaltigen Zelleib unter Aussparung des Kerns bei farblicher Betonung des supranukleären Zellteils SDH Aktivitäten nachweisen. In den Fällen in denen der „intracytoplasmic duct (Lim, 1970 *b*) in gleicher Ebene mit dem übrigen Zellteil dargestellt werden konnte (Abb. 3 *b*) zeigte sich eindeutig das Fehlen von Formazangranula in dieser intrazellulären Hohlraumbildung. Eine geringe, aber stetige SDH Aktivität zeigte sich im bindegewebigen Anteil des Limbus spiralis.

Die Stria vascularis blieb in allen Präparaten durchweg negativ Das Ligamentum spirale zeigte besonders hinter dem Epithel der Prominentia spiralis und oberhalb des Ansatzes der Reißner Membran eine eindeutige Färbung, sowie eine deutliche, wenn auch weniger intensive Tingierung in allen übrigen Bereichen wobei vereinzelte, fibrocytenähnliche Zellen durch stärkere Farbstoffablagerungen hervorgehoben waren.

Im Epithel des Sulcus externus und der Prominentia spiralis konnten keine Aktivitäten nachgewiesen werden.

In den Kontrollversuchen mit Formolpräinkubation zeigte sich lediglich im Bereich des



Abb. 4. SDH-Reaktion am Corti-Organ des Meerschweinchens nach Einwirkung von weißem Rauschen 63 h mit 110 dB. (*a*) Abschwächung der Reaktion in inneren u. äußeren Haarzellen. 570. (*b*) Äußere Haarzellen mit Erhaltung der Depots in der Zona intermedia u. den infranucleären Zellbereichen. Nervenendigungen positiv. 1 420. (*c*) Innere Haarzelle. Erhaltung des Depots in der Zona intermedia. Nervenendigungen und Nervenfasern positiv. Tunnelspiralbündel ebenfalls positiv. 1 420.

Ligamentum spirale mit Ausnahme der Gegend hinter der Prominentia spiralis und oberhalb des Ansatzes der Reißner Membran eine deutlichere Farbstoffablagerung. Auch nach Substratauswaschung mit 0.44 M Sucroselösung und substratfreier Inkubation blieb noch ein positiver Anteil in dem beschrieben Bereich zurück. Nach Malonat-Hemmung wurde jedoch auch dieser Teil völlig negativ. Alle übrigen ausgewerteten Strukturen blieben bei

den durchgeführten Kontrollversuchen ohne Reaktion.

Dauerlärmeinwirkung

Die SDH-Reaktionen nach Dauerlärmeinwirkung zeigten in den verschiedenen Präparaten relativ gleichförmige Ergebnisse. In den inneren und äußeren Haarzellen, sowie den dazugehörigen Nervenendigungen und Nervenfasern konnte eine eindeutige Abschwächung der Färbung festgestellt werden (Abb. 4 *a*, *b*, *c*). Hinsichtlich der intrazellulären Verteilung kam es zu keinen eindeutigen Veränderungen. So blieben bei einer Abnahme der Reaktion in den äußeren Haarzellen insgesamt sowohl die Zona intermedia als auch die infranukleären Zellbereiche und die randnahen Bezirke der perinukleären Zone in den entsprechenden Relationen betont (Abb. 4 *b*). Die zugehörigen Nervenendigungen und die beschriebenen perlschnurartigen Farbstoffdepots am Rande der Deiters-Zellen waren deutlich schwächer gefärbt als im normalen Corti-Organ (Abb. 4 *a*). Die inneren Haarzellen waren hinsichtlich ihrer SDH-Aktivität etwa im gleichen Maße abgeschwächt (Abb. 4 *c*). Auch hier blieb eine farbliche Betonung der Zona intermedia bestehen. Die Nervenendigungen unter den inneren Haarzellen färbten sich ebenfalls weniger intensiv; gleiches gilt für die beschriebenen Aktivitäten im Bereich der Nervenfasern in der Lamina spiralis ossea.

Die übrigen bei der Auswertung der normalen Cochlea als negativ oder positiv beschriebenen Strukturen erfuhren hinsichtlich ihrer Färbungsintensität keinerlei Veränderungen. Ein Unterschied der Abnahme der SDH-Aktivität im Cortischen Organ nach der Lärmeinwirkung der verschiedenen Windungen zueinander konnte nicht eindeutig nachgewiesen werden.

DISKUSSION

Die Anwendung der Perfusionsmethodik zum histochemischen Nachweis mitochondrial gebundener Enzyme bei der Untersuchung von Veränderungen nach Lärmeinwirkung auf der Ebene der Stoffwechselvorgänge in der Cochlea bietet u. E. eine Reihe von Vorteilen gegenüber anderen Methoden.

Die Diffusion des Inkubationsmediums und seine Reaktion mit dem Enzym erfolgt unter intravitalen Bedingungen. Daher ist die Ausschaltung ortsunrichtiger Ablagerungen von Farbstoffdepots durch Enzymdiffusion bei gebundenen Enzymen weitgehend möglich. Außerdem kann nach Beendigung der Reaktion die Fixation des Gewebes praktisch intra vitam erfolgen. Dadurch und im Verein mit der Anwendung neuerer Kunststoffeinbettungen anstelle des ungünstigen Gelatineverfahrens kommt es zu verbesserter Strukturerhaltung, die günstigere Bedingungen für die Auswertung und Dokumentation der Versuchsergebnisse schafft.

Unsere Befunde stimmen im wesentlichen mit den Untersuchungen Spoendlins & Baloghs (1963 *a*, *b*, 1964) überein. Auch in unseren Schnitten blieben die Stria vascularis und das Ganglion spirale eindeutig negativ, obwohl sie SDH in großen Mengen enthalten (u. a. Vosteen 1956 *a*, *b*, *c*). Spoendlin & Balogh erklärten diesen Befund mit einer Diffusionsbarriere zwischen Ligamentum spirale und Stria vascularis, die die freie Diffusion des Inkubationsmediums aus den weiten intercellulären Spalten des Ligamentum spirale in das Gewebe der Stria vascularis hinein behindert. Durch die eindrucksvollen Untersuchungen der Transportvorgänge in der Cochlea mit Thorotrast durch Ilberg (1968 *a*) konnte diese Vermutung bestätigt werden. Danach waren die Intercellularräume der Stria vascularis sowohl gegen die Endolymphe der Scala media als auch gegen das Ligamentum spirale hin durch Zonula occludentes verschlossen, wodurch die freie Diffusion der als Tracer verwendeten Moleküle verhindert wurde.

Die von Gehrhardt (1961 *a*, *b*) untersuchten Cochleae zeigten demgegenüber eine intensive Farbstoffablagerung in der Stria vascularis und den Zellen des Ganglion spirale. Diese Diskrepanz zu unseren Befunden und den Er-

gebnissen Spoendlins & Baloghs (1963 *a* *b* 1964) läßt sich offenbar durch das im Laufe der Vorbereitung zur Inkubation durchge führte Einfrieren und Wiederauftauen erklä ren. Dabei kommt es nach Geyer (1969) zu Veränderungen an den Membranen die die Diffusionsbedingungen erleichtern. Auf diese Weise könnte eine Überwindung der durch Ilberg nachgewiesenen Penetrationsbarriere möglich werden. Die Gefahr der Enzymdislokation ist dabei jedoch erheblich.

Für die Positivität der Stria vascularis in den ebenfalls mit Hilfe der Perfusionstechnik durchgeführten Untersuchungen von Schätzle & Müsebeck (1962) können wir zunächst keine Erklärung finden.

Das Fehlen von Farbstoffablagerungen in den Zellen des Ganglion spirale unserer Präparate muß zunächst ebenfalls mit Behinde rung der ganglionwärts gerichteten Ausbreitung des Inkubationsmediums erklärt werden.

Der Nachweis von SDH Aktivitäten im Ner vus acusticus mit modioluswärts abnehmender Intensität und geringer aber eindeutiger Formazandepots im weiteren Verlauf des Ner ven bis hin zum Ganglion spirale unter Einbe ziehung des intraganglionären Spiralbündels weist jedoch auf eine begrenzt durchlässige Verbindung zwischen Cortilymphraum und Ganglion spirale hin.

Arnold & Ilberg (1971) fanden einen solchen Diffusionsweg nach Injektion von Thorotrast in die Cisterna cerebellomedullaris entlang des Perineuralspaltes des Nervus acusticus, der nach Untersuchungen von Shanta & Bourne (1963) mit einem mehrschichtigen, endothelähnlichen Epithelschlauch gegen das perineu rale Bindegewebe abgegrenzt wird.

Die intensiven Farbstoffablagerungen in ver einzelten Interdentalzellen weisen auf eine er hebliche SDH Aktivität hin. Beim Nachweis von NADH Diaphorase fand Lim (1970 *a*) ebenfalls massiv positive neben völlig negati en Zellen was der Autor mit unterschiedlichen Stoffwechselniveaus erklärte, die durch mitierende Faktoren der Glykolyse reguliert werden könnten. Nach ultrastrukturellen Be funden (Lim, 1970 *b*) sind in Interdentalzellen mit intracytoplasmatischem Gang u. a. die Mitochondrien zahlreicher und besser entwickelt als in solchen ohne Gang.

Die positiven Interdentalzellen unserer Präparate zeigen teilweise unabhängig vom Zellkern größere Aussparungen des ansonsten in allen Anteilen einschließlich Phalanx (Lim, 1970 *b*) stark gefärbten Zellkörpers, die den beschriebenen Gängen entsprechen könnten. Da über die zur Membrana tectoria hin ge legene Öffnung des „intracytoplasmic duct Sekretion von Material beobachtet wurde (Lim, 1970 *b*) das nach Ansicht mehrerer Autoren für die Membrana tectoria bestimmt ist (Belanger 1953 Iurato, 1962 Ilberg, 1968 *b* Lim, 1970 *b*) könnte es sich hier um einen durch verschieden starke Sekretionstätigkeit bedingten unterschiedlich hohen Verbrauch an Energie und Grundbausteinen handeln.

Das Inkubationsmedium müßte entspre ched der von Ilberg (1968 *b*) verfolgten Thorotrastdiffusion aus der Perilymphe der Scala tympani und vestibuli in die Interzellularräume des Limbus spiralis und von dort ohne Behin derung durch die Basalmembranen (Ilberg, 1968 *b*) in die Interdentalzellen gelangen.

Die geringen, aber regelmäßigen SDH-Aktivitäten im bindegewebigen Anteil des Limbus spiralis, in dessen Stromazellen in den Abbildungen Ilbergs (1968 *b*) zahlreiche Mitochondrien gezeigt werden, spricht für eine gewisse Stoffwechselaktivität in diesem Be reich. Da hier eine hohe Resorptionsrate von Thorotrast beobachtet wurde, wird die Resorption von Perilymphe in diesem Bereich für möglich gehalten (Ilberg, 1968 *b*).

Die massiven SDH Aktivitäten in den inne ren und äußeren Haarzellen sind bekannt und sprechen für ihre intensive metabolische Aktivität. Sie wurden in etwa der gleichen intra zellulären Verteilung bereits bei Vosteen (1956 *a* *c*) beschrieben. Die Stützzellen der äußeren Haarzellen jedoch, denen vielfach ebenfalls eine erhöhte Stoffwechselaktivität zu geschrieben wird (Spoendlin & Balogh, 1963 *a*, *b* 1964), zeigten in unseren Präparaten le

diglich am Zellrand unterhalb der Basis der äußeren Haarzellen perlschnurartig aneinandergereihte Farbstoffpunkte. Da dies recht genau der Lage der völlig von Plasmalemm und Cytoplasma der Deiterszellen umgebenen äuß ren Spiralfasern entspricht (Spoendlin & Balogh, 1963 *a b*) muß man annehmen daß es sich hier um eine Darstellung von SDH in diesen Nervenfasern handelt. Die D iterszellen selbst weisen demnach keinerlei Farbstoffabla gerungen auf was den Befunden von Spoendlin & Balogh (1963 *a b* 1964) Gehrhardt (1961 *a b*) und Nakai & Hilding (1968) widerspricht. Auch die inneren Stützzellen zeigen keine Formazandepots.

In den Nervenendigungen an der Basis der äußeren und inneren Haarzellen fanden wir intensive Färbung in Übereinstimmung mit Vosteen (1960) und im Gegensatz zu Gehrhardt (1961 *a b*) und Spoendlin & Balogh (*1963 a b 1964*)

Wie in den Untersuchungen Spoendlins & Baloghs (1963 *a b* 1964) wurden auch bei uns im Bereich des Ligamentum spirale oberhalb des Ansatzes der Reißner Membran deutliche Aktivitäten gefunden Takahashi & Kimura (1970) konnten bei elektronenmikroskopischen *Arbeiten am Rhesusaffen in dieser Zone* ... mitochondrienhaltige Fibrocyten demon ...eren wiesen aber daraufhin, daß der Reichtum dieser Zellen an Organellen bei kleinen Tieren geringer ist, was sich mit den Beobachtungen Spoendlins & Baloghs (1963 *a b* 1964) deckt. Letztere schreiben diesem Be*reich wichtige Funktionen bei der Perilymph*resorption oder -sekretion zu.

Die Färbung von Teilen des Lig. spirale nach Formolpraeinkubation und substratfreier Inkubation nach Substanzauswaschung mit Ausnahme der Gegend hinter der Prominentia spiralis und der der Scala vestibuli benach*barten Bereiche weist auf einen gewissen un*spezifischen Charakter hin Die übrigen positiven Strukturen scheinen nach Auswertung der Kontrollversuche spezifische Aktivitäten nachzuweisen.

Vosteen (1958) fand nach Dauerschalleinwirkung mit einem Sinuston von 2 000 Hz ... 70 dB nach 4–5 Tagen und bei 85 dB n... 2 Tagen Veränderungen in den äußeren Ha...zellen die auf einen bestimmten Bezirk ... Basilarmembran beschränkt waren. Di... Schädigungen ließen sich schematisch ... mehrere Stufen gliedern wobei eine Skala ... Aktivitätsverlust in den Nervenendigun... über stärkere Abnahme der Färbung der Z...len selbst bis zum völligen Aktivitätsverl... und histologischer Schädigung durchlau... wird

Rein histochemisch korrelieren unsere ...funde mit diesen Ergebnissen gut. Die *fe*...lende enge Lokalisation der Schäden, auf ... Windungen bezogen läßt sich für unsere Pr...parate durch das verwendete Breitband...räusch erklären.

Unser Beschallungsmodus wurde entsprec...end den Verhältnissen am Lärmarbeitspl... *eingerichtet. Er unterscheidet sich von de...* Vosteens erheblich dadurch, daß wir zwisch... die einzelnen Belastungsphasen 15 Stund... lange Pausen einlegten. Wir finden denno... bei wesentlich längerer stärkerer Beschallu... im Verhältnis zu den Versuchen Vostee... keine sicheren histologischen Veränderung... *im Sinne von lichtmikroskopisch faßbar...* Schädigungen des Zellkörpers. Daraus ist a...zuleiten, daß selbst nach stundenlanger stä...kerer Beanspruchung der Phonorezeptor... durch eine Lärmpause eine Erholung etwa i... Sinne der Auffüllung eines Stoffwechseldef...zits möglich ist. Die erhebliche Bedeutung d... *Erholungsphase bei Dauerlärmeinwirkung wi...* dadurch unterstrichen. In unseren Präparate... finden wir jedoch einen deutlichen Aktivitäts...abfall auch in den inneren Haarzellen die be... Vosteen frei von Veränderungen blieben. Da... scheint der erstmals von Spoendlin & Balog... (1963 *a, b* 1964) geäußerten Ansicht zuzustim...men *daß die inneren Haarzellen eine gering...* Stoffwechselreserve als die äußeren besitze... und daher bei der in unseren Versuchen ins...gesamt verlängerten Belastungsdauer doch eine Stoffwechselschädigung zeigen da s... nicht in gleichem Maße wie die äußeren Haar...

zellen Energiereserven durch Stoffwechselnebenwege mobilisieren können.

Feinstrukturelle Untersuchungen Spoendlins (1958, 1970, 1971) zeigen bei kurzzeitiger Belastung mit 100–130 dB „weißem Rauschen typische Veränderungen der Mitochondrien *zuerst in den Nervenendigungen* und später in den Haarzellen mit Auftreten von zahlreichen osmiophilen Einschlüssen in den Lysosomen der Zona intermedia als Ausdruck eines degenerativen Abbauprozesses. Wegen der mitochondrialen Bindung der SDH könnten derartigen Veränderungen mit Verminderung der SDH-Aktivität bereits einhergehen

Herrn Prof Dr med. habil. H. G Dieroff, Oberarzt der Univ HNO-Klinik Jena, wird für die Erstellung des Beschallungsprogramms herzlich gedankt.

SUMMARY

In the normal cochlea of the guinea pig the SDH has been demonstrated by a perfusion method. The enzyme activity was localized exactly as in the results after incubation of sections and small tissue samples with the notable exception of a negative reaction in the stria vascularis and in nerve cells of the spiral ganglion. The SDH activity is significantly reduced in the outer and inner hair cells and the nerve endings of animals which were exposed to white noise of 110 dB for 63 hours (9 h noise, 15 h rest, interval at Saturday and Sunday). The decrease of enzyme activity was not restricted to any particular area of the cochlear duct. The results are discussed.

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DENSITY OF MUCOUS GLANDS IN A BIOPSY MATERIAL OF CHRONIC SECRETORY OTITIS MEDIA

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Abstract Biopsies were taken from the anterior part of the promontory in the course of tubulation through a paracentesis opening in 85 ears affected with chronic secretory otitis media in the secretory stage from 54 patients, mostly children. The specimens were stained by the PAS-alcian blue whole-mount method, and on each biopsy the number of glands was counted, their area measured directly and their density calculated. Glands were found in all ears but two from which the specimens were very small. The density varied within wide limits, from 1 to 31 glands per mm². In most ears the density was 3–10 glands per mm². The mean density in the entire material was 6.7 glands per mm², gland count per biopsy 7.5. In all, 743 glands and 105 mm² mucosa were investigated. 92.7% of the glands were active, 5.7% were transitional types, and only 1.6% were degenerated. In cases with large quantities of mucus and thickened mucosa the density as well as the number of glands per biopsy were greatest. There was a relationship between the severity of the secretory otitis in the secretory stage and the density of mucous glands. This further stresses that the mucous secretion which accumulates in the middle ear is an active product of the mucous glands.

Research into the mucous elements in the Eustachian tube and middle ear has been greatly intensified during recent years, not least because of their significance in understanding the pathology and pathogenesis of chronic secretory otitis media.

Studying biopsies from 40 ears affected with secretory otitis media, removed from the mucosa inferiorly and anteriorly to the round window Bendek (1963) found glands in 22% of the cases. Sadé (1966) found glands in biopsies of the promontorial mucosa in all his 20 cases of secretory otitis, whereas Gundersen (1971), studying 189 biopsies removed anteriorly to the round window found no glands in any case. Paparella & Lim (1967) reported on gland-like structures in biopsies from the mastoid process in three patients with secretory otitis.

In autopsy materials of secretory otitis Sadé (1966) observed glands in the middle ear in three cases and de Moura & Hayden (1969) in one. All these studies (except Gundersen's) were based on histological sections. Previous biopsy as well as autopsy materials have not been subjected to determination of the density of glands or differentiation of the various types or secretory stages of glands.

For the study of mucous elements in the middle ear we have used whole-mount methods, preparing the mucosa in toto, counting *all glands, making direct measurements of the* mucosal area, and calculating the glandular density. In 1 patient with mild secretory otitis media we had found (Bak Pedersen & Tos, 1971) by post-mortem study of 370 mm² mucous membrane from the osseous Eustachian tube and middle ear 488 glands.

The glands were in different secretory stages (Tos & Bak-Pedersen, 1972). 1) Active glands with narrow ducts without stagnation of mucus and with well-preserved secretory epithelium. 2) Transitional varieties with dilated ducts and stagnant mucus, loss of the

secretory epithelium which however was preserved in places. 3) Degenerate, inactive glands, with pronounced cystic dilatation of the ducts and total loss of the secretory epithelium On this basis, we advanced a new secretory pathogenesis of secretory otitis: Aetiological factors give rise to metaplasia of the middle-ear mucosa with formation of mucous glands (developmental stage) which condition lasts for several months. When the formation of the glands is completed, they secrete mucus (secretory stage) even though the aetiological factor which has caused their formation has ceased to exist. When most glands have started to degenerate the production of mucus decreases, and the disease improves spontaneously (degenerative stage), provided that it has not caused irreparable damage i.e. adhesive otitis.

Foetuses and newborn infants have no mucous glands in the middle ear or osseous Eustachian tube (Buch & Balslev Jørgensen, 1964 Tos, 1970 1971). By studying almost the entire mucosa from the osseous tube and middle ear from 45 clinically normal adult temporal bones, Bak Pedersen & Tos (1972) found that 41 (91) had glands in the mucosa. However these glands were as a rule resent in small numbers, less than 20 in 45% s than 40 in 65% and less than 60 in 85% f the cases. Most of the glands were degenerate. The mean density within the entire material was 0.53 gland per mm² Thus, although there may be glands in clinically normal middle ears, they are probably not a normal component of the mucosa, but have arisen because of previous pathological actions upon the mucosa.

MATERIAL AND METHOD

The material comprises 85 ears from 54 patients treated by tubulation for chronic secretory otitis media. One patient was 2 years 16 were 3–5 years, 26 were 6–10 year nd 8 were 11–16 years of age. Three were adult Under general anaesthesia, after paracentesis and suction of mucus through the paracentesis opening, a biopsy specimen of the mucosa was taken anteriorly on the promontory at the junction to the anterior part of the hypotympanum. In about three-quarters of all cases one piece of mucosa was removed, in the remaining cases two or more small pieces. It was endeavoured to make th biopsy comprise the full thickness of the mucous membrane. After fixation in formol alcohol and staining by the PAS-alcian blue whole mount method the preparations were cleared in anise oil, microdissected, and smoothed under the stereomicroscope, placed in a chamber filled with anise oil-colophonium, and sealed with paraffin. In each biopsy all glands were counted in the stereomicroscope, magnification 40× the area of the biopsy was measured directly and the density was calculated. The number of active and of degenerate glands as well as of the transitional stages were determined separately for each biopsy

RESULTS

All glands were tubular the majority consisting of one tubule running from the orifice on the epithelial surface either vertically or obliquely down into the mucosa (Fig. 1). Besides this, there were several branched glands, consisting of one excretory duct into which two tubules debouched. More rarely there were larger glands having several tubules. The various types of glands, their size and site, have been described previously in an autopsy specimen (Bak Pedersen & Tos, 1971). In the present biopsy material we found the same types and approximately the same size of glands.

On the whole, the density of glands was *high, but there were marked variations* (Table I) Only 2 cases were found to contain no glands. In most of the ears the density was 3–10 glands per mm² but in others a very high density was observed. The maximum density was 31 glands per mm² For all 85

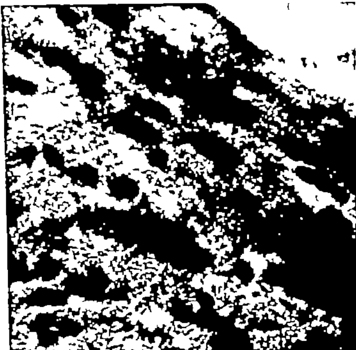


Fig 1 A biopsy showing a great density of small tubular active glands the orifices of which are visible. PAS-alcian blue-stained whole mount, 200.

ears the mean density was 6.7 glands per mm² the mean area of the biopsy 1.3 mm² and the mean number of glands per biopsy 8.7 In all, 743 glands were found within the entire material and 105.3 mm² of mucosa were investigated.

The size of the biopsy influences the reliability of the density determination. In the 2 cases in which no glands were found, the mean area was small (Table I). The area of the smallest biopsy was 0.2 and that of th largest 6.7 mm² (Table II). In the group of small biopsies the density might vary widely Within the group in which the area of the biopsy was 0.2–0.4 mm² the highest density was 31 glands per mm² but there was also one preparation with no glands. Within the group in which the biopsy area was 0.5–0.9 mm² there was also a marked variation in density and in the number of glands per biopsy However a biopsy which is 0.5 mm² can afford a fairly reliable picture of the glandular density the mean density in this group being 5 7 glands per mm² In most ears the biopsy was 1 mm² or larger The reliability of the density determination was considerably increased in biopsies of this size in particular the mean gland count per biopsy was large.

The highest gland count, in a biopsy of 3 8 mm² was 91 glands, corresponding to a density of 24 glands per mm² (Table II). In 20 ears the gland count per biopsy exceeded 10 in 5 ears it exceeded 30 The mean number of glands per biopsy in cases where the area was 3 mm² or over was very large.

Out of a total of 743 glands 689 (92.7%) were active, the entire tubule being lined with well-preserved secretory epithelium, with no dilatation of the duct and no stagnation of mucus in the duct (Fig. 1). 42 glands (5 7%) were of the transitional type, with incipient stagnation of mucus and incipient dilatation of the duct system, but having fairly well preserved secretory epithelium. Only 12 glands (1 6%) were completely degenerated, cystic, with dilated ducts, filled with stagnant mucus, and showing total disappearance of the secretory epithelium. The transitional and degenerate glands were found especially in biopsies

Table I. *Number of ears in each density group the corresponding mean density area of biopsy and number of glands per biopsy*

Density group (glands/mm²)	No. of ears	Mean density	Mean area (mm²)	Mean number of glands
0	2	0	0.6	0
1–2	16	1.8	1.0	1.6
3–5	29	3.8	1.3	5.4
6–10	23	7.6	1.3	9.5
11–15	9	13.1	1.5	19.8
16–20	4	17.5	1.0	17.2
21–40	2	27.5	2.0	48.0
Total	85	6.7	1.3	8.7

in which the gland count was high and which also contained many active glands. The very high percentage of active glands indicates that the disease has been in the secretory stage and fully explains the presence of mucus in the middle ear

By tubulation the amount of mucous discharge could be determined (Table III) In cases with little or moderate discharge the mean density and mean number of glands per biopsy were lower than in cases where the middle ear was filled with mucus. In the group with but little secretion there were several cases in which the amount of secretion was minimal, in a few merely in the form of film of mucus on the mucosa. All ears with a little mucus were found to contain glands. Within the group with moderate quantities of secretion only one case did not exhibit glands.

Table II *Relationship between size of biopsy and variation in density as well as variation in number of glands per biopsy*

Size of biopsy (mm²)	No of ears	Density			Number of glands per biopsy		
		Max.	Min.	Mean	Max.	Min.	Mean
0.2–0.4	6	31	0	10.5	5	0	[illegible]3
0.5–0.9	27	18	0	5.7	11	0	3.4
1–1.9	36	18	1	6.3	34	1	7.8
[illegible]–2.9	11	13	1	5.3	32		11
3–3.9	3	4	4	12.3	91	1	43.3
5–6.7	2	14	5	9.5	68	34	[illegible] 0

Similarly there was one case without glands in the group with ample secretion. If the biopsy had been larger or if it had been taken from another site, it would no doubt have shown glands in these two cases too. Thus, there was a relationship between the quantity of secretion and the density of glands and thus between the severity of secretory otitis in the secretory stage and the gland density

The thickness of the mucosa was assessed during the tubulation (Table IV) In cases where the mucosa was not thickened the density of glands as well as the number of glands per biopsy were lowest. The lower average number of glands per biopsy than the average density indicates that the biopsies were small, as is comprehensible since it is difficult to take a biopsy from a thin mucosa. Within this group there was one ear in which no glands were found. In cases having a slightly or moderately thickened mucosa the density as well as number of glands per biopsy were high, even higher than in cases with a greatly thickened mucosa among which there was also one ear without glands. In the group with a greatly thickened mucosa the mean density as well as the mean number of glands per biopsy were surprisingly low A possible explanation is that they had oedema which caused the thickening of the mucosa. In cases with highly proliferating, almost polypous granulating mucosa, where small, round polyps were removed from the mucosal surface at the time of taking the biopsy and could then be examined *in toto* there was a fairly large mean number of glands per biopsy (Table IV). Often, but not invariably, there were small young, active glands in the polyp which was covered with secretory epithelium, indicating marked proliferation of the mucosa and metaplastic new formation of glands and goblet cells. However there were also cases of polypous mucosa whose surface was only partially covered with goblet cells and in which glands were not yet found. Possibly such polyps had arisen recently and the formation of glands had not yet started.

DISCUSSION AND CONCLUSION

On the basis of the secretory pathogenesis Tos & Bak Pedersen (1972) have categorized secretory otitis into the developmental stage, the secretory stage, and the degenerative stage. As mucus was found in all the ears, in varying quantity it is true, the disease must have been in the secretory stage at the time that the biopsies were taken. The density of glands was relatively great. In 92.7% of the cases the glands were active and producing mucus. There is little doubt that the mucus which accumulates in the middle ear is an active product of these glands and of the goblet cells. The density proved to be widely varied, from 1 to 31 glands per mm² and this was due only partially to a relatively small biopsy True, it was endeavoured to remove the biopsy from the same site in all cases, but the density need not be the same in all ears in the same area. In the autopsy specimen described previously the density varied very much between the different parts of the tympanic cavity being greatest in the hypotympanum anteriorly (Bak Pedersen & Tos, 1971), but this does not prove that the density is greatest at this site in all cases of secretory otitis. The main cause of the variations in density must be differences in the severity of the disease, which during the secretory stage depends upon the secretory capacity of the glands (their number and size), upon the secretory activity of the active glands, upon tubal function, and upon ciliary function which conveys the produced mucus to the rhinopharynx. In the mildest cases, with a small number of glands and a good tubal as well as ciliary function the condition will presumably never progress to an accumulation of mucus and clinical symptoms. In the most severe cases, with a great density of glands, the mucus production will continue for years, in spite of a properly functioning drainage, and this will require several tubulations. This is confirmed by the present demonstration of a greater mean density and considerably larger number of glands per biopsy in cases with much mucus in the middle ear and with major mucosal changes. Another important factor influencing the variation in density is the time of taking the biopsy Metaplasia of the mucosa and the formation of glands must take place gradually presumably in the course of a long period. If a biopsy is taken at an early stage of the disease there will presumably still be little density of glands, but it may continue to increase. In several cases we found signs that the glands were young and very small, suggesting that gland formation had not yet culminated and ceased. The very low percentage of degenerated glands also indicates that all ears were in the secretory stage and that the degenerative stage had not yet started. In the present biopsy material there is still a theoretical possibility that the density may increase further

The total number of glands in each middle ear may be calculated to a certain degree: If

Table III *Relationship between quantity of secretion during tubulation and mean density of glands as well as mean number of glands per biopsy*

Quantity of secretion	No. of ears	Mean density of glands/mm²	Mean number og glands per biopsy
Small	25	5.2	5 8
Moderate	13	5.5	5.8
	47	7.6	10 9

Table IV *Relationship between thickness of mucosa during tubulation and mean density of glands as well as mean number of glands per biopsy*

Thickness of mucosa	No. of ears	Mean density of glands/mm²	Mean number of glands per biopsy
Not thickened	7	3.0	2.3
Slightly thickened	37	6.7	7.9
Moderately thickened	17	8.5	12.6
Considerably thickened	15	5.6	5.9
Polypus, granulating	9	7.5	14.5

the area of the middle-ear mucosa is 400 mm² and the mean density is five glands per mm² there will be 2 000 glands in the middle ear and this represents a quite appreciably secretory capacity However very marked individual variations may be expected in area as well as in total gland number

The present results confirm and supplement earlier findings by Bendek (1963) Sadé (1966) and by Paparella & Lim (1967) who demonstrated glands in the mucosa in secretory otitis, but are at marked variance with Gundersen (1971) who did not observe glands in any of his cases. This difference must be due to a difference in technique Gundersen took his biopsies just anterior to the niche of the round window and smeared the material on the slide. In other words, these were not histological sections. Therefore, the failure to demonstrate glands does not prove that none were present The whole-mount method demonstrates its superiority in the study of the mucous elements of mucous membranes. By this method it is possible not only to ascertain the presence of the glands, but also to examine each uncut gland separately and in this way determine the shape size, and secretory capacity of the glands, their number and density

Beside the mucous glands there are in the epithelium goblet cells. Owing to epithelial metaplasia their density is increased in secretory otitis. In the great majority of our biopsies we found a great density of goblet cells, but a quantitative study of their density cannot be evaluated until determinations of the goblet cell density in the middle ears of normal children have been carried out We are at present performing quantitative studies of the goblet-cell density in the middle ear under normal as well as under abnormal conditions.

ZUSAMMENFASSUNG

Bei 85 Ohren von 54 Patienten (vorwiegend Kindern) mit Otitis media chronica im Sekretionsstadium wurden bei der Tubulation durch die Paracentheseöffnung Schleimhautbiopsien vom vordersten Teil des Promontoriums entnommen, und nach PAS-Alcianblaumethoden der Ganzpräparate gefärbt. An jeder Biopsie wurde die Anzahl der Drüsen bestimmt, die Fläche gemessen und die Dichte berechnet. Nur bei zwei Ohren, wo die Biopsien klein waren, wurden keine Drüsen gefunden aber bei allen anderen. Die Dichte variierte von 1 bis 31 Drüsen/mm² Bei den meisten Ohren wurde eine Dichte von 3 bis 10 Drüsen/mm gefunden Die durchschnittliche Dichte des ganzen Materials var 6 7 Drüsen/mm² Anzahl der Drüsen per Biopsie 7,5 Im ganzen wurden 743 Drüsen und 105 mm² Schleimhaut untersucht. 92,7 der Drüsen waren aktive 5 7% Übergangsformen und nur 1,6% degenerierte Drüsen. Bei den Fällen mit viel Schleim und dicker Schleimhaut war die Dichte der Drüsen und Anzahl der Drüsen per Biopsie am grössten Es wurde ein Zusammenhang zwischen Schwerheitsgraden der sekretorischen Otitis im Sekretionsstadium und der Dichte von Drüsen bewiesen, was auch wieder beweist, dass der Schleim, der sich im Mittelohr bei der sekretorischen Otitis ansammelt, ein aktives Produkt der mukösen Drüsen ist.

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THE ROLE OF THE SURFACE TENSION AND THE CONTACT ANGLES OF PERILYMPH IN STAPES SURGERY

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Abstract. Physical aspects of stapes surgery are discussed. In order to determine the wettability of possible materials for the prosthetic use the advancing contact angles of perilymph on vitallium and Teflon were measured and were found to be (62° ± 3°) and (101 ± 4°) respectively As far as this physical factor is involved, the better choice is Teflon. In order to facilitate further *in vitro* experiments the surface tension of perilymph samples of 76 otosclerotic ears was measured. The distribution showed a mean value of 50.6 dynes cm with a standard deviation of 3.3 dynes cm

As mentioned earlier (Marquet, 1970) the surface tension of perilymph is a very important factor in the protection of the labyrinth during footplate surgery After stapedectomy the surface tension of perilymph, together with the contact angle of perilymph on the prosthesis, seem to determine the shape of the reparative soft tissue which will obturate the trepanation hole (Marquet et al., 1972). In order to determine the best suitable prosthesis for the stapes a comprehensive study of these factors was undertaken

Behaviour of Perilymph in Contact with Prosthesis

The final result of a surgical intervention depends greatly on the shape of the obturating, reparative tissue. When a grafting material is used, there is some risk of obtaining a muff When no graft is placed, the same complication can occur more frequently if a non-suitable material is used for the prosthesis and if all directions as given in our previous paper are not followed carefully

We have observed that the wettability of the prosthesis and thus the contact angle θ of perilymph on the material used is very important.

Let us first consider the case of $\theta < 90$ (Fig. 1 *a*) The liquid will wet and cover the prosthesis and the tissue growing on the meniscus will form a muff When a suitable material (with $\theta > 90$) is placed carefully (without pushing the prosthesis too far into the perilymph) a more favourable situation is created (Fig. 1 *b*) As described in a previous paper the tissue will now grow underneath the piston and really obturate the opening.

Measurement of Contact Angles

A useful estimate of the wettability of solids by a fluid is the advancing contact angle θ_a. This is the maximum value of θ when a liquid advances over a solid surface, while the receding angle θ is the minimum value when a liquid recedes over a solid surface (Johnson & Dettre, 1969) The advancing angle can be obtained by increasing the volume of a liquid drop resting on a plane solid surface, until the three-phase boundary moves over the sur

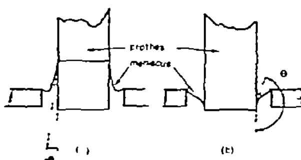


Fig. 1. Shape of the perilymph meniscus: (*a*) contact angle θ of the perilymph on the prosthesis <90°, (*b*) θ>90°.

face (drop method). Values of θ of perilymph on vitallium and polytetra fluoroethylene (PTFE or Teflon) were measured directly on the profile of the drop. The micro syringe which was used to increase the drop volume was kept immersed in the drop during the measurement (see Fig. 2).

As found by Bartell & Björklund (1952) the presence of this fine tip within the drop does not alter the value of the contact angle. The direct measurement of θ was done using a binocular loupe fitted with one goniometer eyepiece.

This technique was chosen because it can be used on solids having small surface area and requires only small amounts of liquid (even less than 1 μl). Contact angles were measured with an instrumental accuracy of

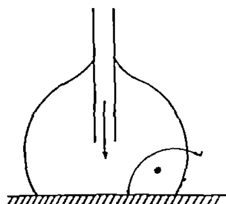


Fig. 2. Technique for obtaining advancing contact angles.

about 2%. Samples from 4 patients were analysed. For the advancing contact angle of perilymph on vitallium we found a mean value (θ) = 62° with a standard deviation of 3° and for perilymph on Teflon (θ) = 101° with a standard deviation of 4°. In both cases the receding angles were very small (< 15°) but could not be determined accurately because of the difficulties in locating the point of contact and in constructing the tangent to the drop profile in the contact point.

From these measurements we can conclude that from a physical point of view Teflon is the better suited material.

Determination of Surface Tension of Perilymph

The surface tension of perilymph accounts for the protection of the labyrinth against waste particles with a density greater than that of perilymph. The knowledge of the value of the surface tension of perilymph is also required to enable further "in vitro" experiments. For this purpose a microtensiometer was developed (Creten et al., 1972) enabling quick routine determination of the surface tension from samples of 0.4 to 0.7 μl with an accuracy of about 2%.

During footplate surgery the perilymph was obtained, after the footplate was perforated, by means of a capillar with an outer diameter of about 0.6 mm and an inner one of about 0.3 mm. From each patient an amount of 0.5 to 2.0 μl was taken in one or more capillars. This amount was transferred into a micro syringe and a known quantity (0.4 to 0.7 μl) was put in the glass receptacle of the microtensiometer. All manipulations including the determination of the surface tension of the sample were performed within a few minutes. The results obtained with samples from 76 patients are given in Fig. 3. All measurements were performed at 22° C.

The distribution has a mean value of 50.6 dynes cm with a standard deviation of 3.3

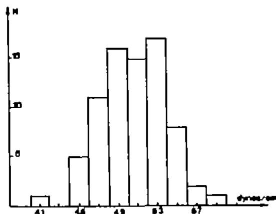


Fig 3 Distribution of the surface tension of perilymph.

dynes/cm. We may assume that the distribution is gaussian as the skewness g_1 and the curtosis g_2 (Snedecor 1956) are both zero within the statistical errors.

$(g_1 = -0.26 \pm 0.28, g_2 = 0.1 \pm 0.5)$

As the patients were under a general anaesthesia called "protected sleep" (Delaruelle & Marquet, 1971) a surgical field with minimal bleeding was obtained, so that the perilymph samples were seldom polluted with blood. From 8 patients more than one sample was taken, one of which was polluted with blood. No detectable alteration of the surface tension of perilymph is found.

RÉSUMÉ

Ce travail se rapporte à l'étude des aspects physiques de la chirurgie de l'étrier. Afin de déterminer le degré de mouillage de différents types de prothèses, l'angle de contact de la périlymphe a été mesuré respectivement sur du vitallium et du teflon. Les résultats furent (62°±3°) et (101 ±4°). Pour autant que ce paramètre physique soit déterminant, préférence est donnée au teflon. Afin de permettre une expérimentation ultérieure (in vitro), la tension superficielle de la périlymphe fut mesurée chez 76 patients opérés d'otosclérose. La distribution donna une valeur moyenne de 50,6 dynes/cm avec une déviation standard de 3,3 dynes/cm.

ZUSAMMENFASSUNG

Die physikalischen Aspekte der Stapeschirurgie wurden besprochen. Um den Befeuchtungsgrad des eventuellen Prothesenmaterials festzustellen, wurde der fortschreitende Kontaktwinkel von Perilymphe auf Vitallium und Teflon gemessen. Die respektiven Ergebnisse waren 62°±3 und 101 ±4. Soweit dieser physikalische Parameter ausschlaggebend ist, ist Teflon zu bevorzugen. Um weitere in-vitro-Versuche zu ermöglichen, wurde die Oberflächenspannung von Perilymphen-Proben von 76 Otosklerose-Patienten gemessen. Die Verteilung ergab einen mittleren Wert von 50,6 dynes/cm mit einer Standardabweichung von 3,3 dynes/cm.

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TRANSTRACHEAL CERVICAL APPROACH FOR OPERATING ON SEVERE INTRATHORACIC TRACHEAL STENOSIS FOLLOWING ASSISTED RESPIRATION

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Abstract This report describes the surgical treatment of 5 patients with severe degrees of intrathoracic tracheal stenosis following long-term assisted respiration. The operation was carried out via a transtracheal approach in the cervical part of the trachea. Using long-handled instruments and local anaesthesia, the circular stenosed area was extirpated endotracheally A cannular prosthesis was inserted and left in position for 4 months. The operations involved no complications, and the results were excellent in all five cases. The effect of surgery was evaluated by spirometry and body plethysmography which were performed before and 6 to 18 months after removal of the prosthesis.

The modern treatment of respiratory failure has saved patients lives to an extent that could never have been imagined earlier A serious complication following respirator therapy in resuscitation is stenosis in the intrathoracic part of the trachea.

Thorax surgeons have in these cases carried out a circular resection of the stenosed tracheal area and then sutured the trachea end to end (Michelson et al 1961 Grillo 1965 1969) This end-to-end method has brought the best results in the resectioning of a tracheal segment with an endotracheal tumour The peritracheal region in these cases has been normal and permitted mobilization and suturing of both tracheal ends. When the same end to-end operation is to be carried out in intrathoracic tracheal stenosis, several serious problems arise.

1 Peritracheal scar tissue and infection
2 The trachea is not easily mobilized for suturing
3 The sutures tend to "cut through"
4 Large blood vessels are often adherent to the trachea
5 Recurrent nerves, partly embedded in the scar tissue, are difficult to identify
6 Recurrent nerves can be injured in the postoperative cicatrization process.

Cases of sternal osteitis following sternal division mediastinitis and rupture of the large blood vessels adherent to the trachea have been reported (Aboulker et al. 1967 Aboulker 1968) treated with the end to-end technique. Even if just one recurrent nerve is injured intra or postoperatively resulting in unilateral recurrent nerve paralysis, the consequences are not agreeable for the patient. Respiratory function tests have shown that unilateral recurrent nerve paralysis means that the tracheal lumen is reduced by one-third Even a successful operation of the tracheal stenosis itself in many cases may bring no relief of the patient s dyspnoea if the result is eliminated by a unilateral recurrent nerve paralysis.

The published series of resection and end-to-end anastomosis, even when carried out by skilled hands, have shown a proportion of mortality (Pearson et al. 1968 Grillo 1969).



Fig. 1. Roentgenogram of intrathoracic tracheal stenosis.

The patient lay on his back with a pillow under the shoulder blades, by which means the intrathoracic part of the trachea was slightly raised cranially. The skin incision was made vertically down to the jugulum. The surgeon then sat down behind the patient's head and made a vertical incision in the trachea, as distally as possible (Fig. 2). The edges of the tracheal incision were retracted. The stenosed ring inside the trachea was infiltrated by a long injection needle. The entire intratracheal stenosed area was then excised, using a knife with a long narrow handle and long handled scissors and tweezers (Fig. 3). The excision was continued until it reached tracheal lumen of a normal size. Sometimes the mediastinum was faintly visible through the thin tracheal wall. The next step was to insert a long and thick silver cannula encased in plastic tubing (Fig. 4). The distal end of the cannular prosthesis must reach below the excised cicatrized length. In some cases the distal end lay just above the carina. The incision was sutured,

MATERIAL AND METHOD

In the Department of Otorhinolaryngology, University Central Hospital, Helsinki, we have developed a method for operating these severe cases of chronic intrathoracic tracheal stenosis (Fig. 1). Five have been treated to date. Table I shows the series and the results.

Owing to the numerous inconveniences of operating on the thoracic portion of the trachea in intubation anaesthesia (Nissen 1961, Woods et al. 1961) all the operations of the present series were performed under local anaesthesia. Preoperatively the patients were given atropin. We used 0.5% Carbocain® for infiltration, even the stenosed area inside the trachea was infiltrated. The mucosal surfaces were anaesthetized with 3% Xylocain®. Dia- ® was used in doses of 5 mg at a time, to a total dose of 45 mg and Silomat® in doses of 20 mg at a time, up to a total of 80 per operation.

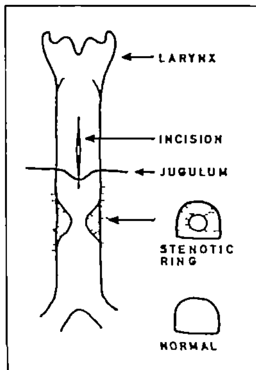


Fig. 2. Schematic appearance of the stenotic ring and the level of the incision.

curves (Popplus, 1969) and flow volume curves (Jordanoglou & Pride 1968)

All 5 patients had spirometrical evidence of airway obstruction during expiration as well as inspiration and flow-volume loops compatible with upper airway stenosis. All patients had normal values for transfer factor arterial blood gases, physiological right–left shunt and distribution tests based on analysis of expiratory CO_2 curves, suggesting absence of significant pulmonary parenchymal disease. One patient (case 2) with a clinical diagnosis of asthma and a history of persistent sputum showed a slight increase in both nitrogen single breath index and arterial-end-tidal CO_2 difference compatible with peripheral airways disease in the other 4 patients these tests gave values within the normal range.

Preoperatively spirometry showed that both expiratory and inspiratory flow were greatly increased in all patients, excepting the patient with asthma (case 2, Table II). Of the 4 patients examined with body plethysmography both before and after surgery all but case 2 showed a remarkable postoperative fall in airway resistance to normal or borderline values. In case 2, surgery was followed by no change in FEV_1 a marked increase in inspiratory flow (FIV%) a reduction of airway resistance by two-thirds to a still definitely pathological value and a change in the shape of the flow-volume curve from the type of upper airway stenosis to the type of peripheral airways obstruction (Jordanoglou & Pride 1968) In this case the upper airway stenosis had presumably prevented expiratory airway collapse before the operation, and surgery resulted in a partial shift of the site of obstruction to air flow from the area of the tracheal stenosis towards the periphery

Analysis of respiratory function showed severe upper airway stenosis before operation in all 5 cases. In 4 cases, surgery re-established normal or almost normal flow conditions In the asthmatic patient (case 2) the effect of surgery was somewhat difficult to evaluate owing to the variable peripheral airways obstruction there was, however indirect physiological evidence of a marked reduction of the degree of upper airway stenosis also in the case.

Table II *Results of spirometry and body plethysmography before and 6 to 28 months after removal of the prosthesis*

Case no	Sex	Age (yrs)	Height (cm)	Parameter of respiratory function	Before surgery	After surgery
1	♀	23	172	VC	3.38	[illegible]
				FEV_1	1.29	[illegible]
				FEV%	39	75
				FIV	42	90
				Rt	–[a]	4.2
				Rt TGVm	–	13.4
2	♀	21	161	VC	3.57	[illegible]
				FEV_1	1 10	1.30
				FEV%	32	41
				FIV%	36	71
				Rt	28.8	9.5
				Rt TGVm	131 4	42.4
3	♀	45	154	VC	2.92	2.33
				FEV	1.39	[illegible]
				FEV%	49	82
				FIV%	54	100
				Rt	17 4	1 4
				Rt TGVm	56.0	3 1
4	♂	38	173	VC	4.22	4 60
				FEV_1	1.69	3 10
				FEV%	40	79
				FIV%	34	86
				Rt	19.9	3 0
				Rt TGVm	94.2	10 5
5	♀	20	164	VC	3.74	4 19
				FEV	1.56	[illegible]
				FEV%	48	91
				FIV%	57	84
				Rt	5.9	[illegible]
				Rt TGVm	4 0	4 4

VC and FEV_1 in l BTPS. Rt in cm H_2O/l/s [illegible] in cm H_2O s.
[a] Body plethysmography not possible due to immobilization of fractured leg.

DISCUSSION

Intubation anaesthesia could not be used because of the shortage of space in the trachea and in order to avoid the risk of the anaesthetic gases being forced into the mediastinum by overpressure.

The method presupposes the use of [illegible]

handled instruments for the transtracheal intrathoracic operations. We realized there was a risk of acute haemorrhage in the operative field. Such a haemorrhage, if massive, would be difficult to control. In no single case, however did a profuse bleeding occur. This was probably because the operation was not performed while granulation was in progress, since we waited until cicatrization was complete and mature in the form of a totally fibrotized and almost avascular scar tissue. At the same time we applied anaesthesia so as to ensure the least possible irritation that might cause coughing. Silomat® and Diazepam® in large doses proved to be well-suited for this purpose.

The cannular prosthesis, on completion of the operation, was inserted into the trachea without in any way covering the surfaces of tracheal wounds caused by scar excision. During the 4 months the cannular prosthesis was in position the wound surfaces were completely epithelialized.

A straight prosthesis of the Aboulker type (Aboulker 1968) was used for 2 patients (cases 2 and 4). This prosthesis had been successfully used by the present author (Grahne 1971) in operations for subglottic laryngeal stenosis. In case 2, because of difficult respiration, the prosthesis had to be exchanged for a cannular prosthesis on the very day of the operation. In case 4 the exchange had to be effected only $3\,^{1}/_{2}$ months after the operation since the distal end of the straight prosthesis had produced a new tracheal stenosis. A later re-operation of the new stenosis using the cannular prosthesis was successful. The prosthesis in the intrathoracic part of the trachea must necessarily follow the natural, slightly curved shape of the trachea, and the gently curved cannular prosthesis used in most cases of the present series suited the purpose admirably.

The results have been excellent. It is the experience of the surgical member of the team (B. G.) that the Aboulker prosthesis, which is first-rate in subglottic stenosis, cannot be used intrathoracically because of the slight curve in this part of the trachea.

ZUSAMMENFASSUNG

Es wird die chirurgische Behandlung von fünf Patienten mit schwerer intrathorakaler Trachealstenose im Gefolge von langfristiger Respirator Behandlung beschrieben. Die Operation wurde auf transtrachealem Wege im zervikalen Abschnitt der Trachea ausgeführt. In Lokalanaesthesie wurde mit Hilfe von langschäftigen Instrumenten die narbige Ringstenose endotracheal exstirpiert. Es wurde eine Kanülenprothese eingelegt und vier Monate lang liegengelassen. Die Operationen verliefen ohne Komplikationen, und die Resultate waren in allen fünf Fallen ausgezeichnet. Der Erfolg der chirurgischen Behandlung wurde mit Spirometrie und Korperplethysmographie kontrolliert, die vor der Operation sowie 6–28 Monate nach Entfernung der Prothese vorgenommen wurden.

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EFFECT ON CARIES SUSCEPTIBILITY AFTER SURGICAL TREATMENT OF DROOLING IN PATIENTS WITH NEUROLOGICAL DISORDERS

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Abstract In 10 patients with neurological disorders and drooling, retroposition of the submandibular and ligation of the sublingual ducts was performed in order to reduce the drooling. This study shows the effect of the operation on the caries activity Examination of the dental status was made before and one year after the operation. In some cases an enhanced susceptibility to caries was found, measured as increase in white spot lesions or transformation of these lesions into caries cavities. With good prophylactic measures the risk of increasing caries activity would not appear as a major contra-indication to the surgical treatment described.

Drooling can be seen in persons with neurological diseases, e.g. cerebral palsy Drooling has been treated either with anticholinergic drugs or surgically to reduce saliva production (Goode & Smith, 1970· Enfors & Lundberg, 1968). Some authors have described operative methods to reduce the accumulation of saliva in the anterior part of the mouth. Laage-Hellman (1969) describes a surgical method for retropositioning of the submandibular ducts. The operation was performed on a few drooling children with cerebral palsy A similar operation was described by Wilkie (1967) who in a few cases of drooling children made a retroposition of the parotid ducts. In a second stage, bilateral extirpation of the submandibular glands was performed

A modification of the surgical technique described by Laage Hellman (1969) was elaborated (Ekedahl, 1973) to control the drooling. In this technique the duct from the submandibular gland was led to the palatal arches and the ducts from the sublingual glands were ligated.

Surgical treatment involving changes in salivary secretion may increase the susceptibility to oral disease since the composition and rate of secretion of saliva is of importance to counteract the caries provoking effects of food debris and bacteria-rich plaques retained on the teeth.

The present investigation was performed to study the effect of the operation on the caries activity A preliminary report of these data has been presented (Ericson et al., 1971).

MATERIAL AND METHOD

The investigation was made on 5 male and 5 female patients, 7 to 26 years of age. Clinical and laboratory data were collected before and one year after operation.

Oral examination

Caries index, dental plaque index and gingival index were recorded. The dental status was checked with an explorer and mirror in a dentists chair under good lighting conditions. No roentgenological examination was made

Table I *Caries plaque and gingival index of drooling persons before and after operation a.m. Ekedahl (1973)*

			Caries index						White spot lesions		Plaque index		Gingival index	
			DMFT		DMFS		Westin							
	Age	Sex	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
K. A.	10	♀	2	4	2	4	0.02	0.04	0	0	2..5	1 1	1	1
C. P	11	♀	6	11	7	12	0 06	0.1.	0	34	1.5	1.3	1	1 2
B. J	18	♀	26	27	64	69	0.55	0.60	0	0	2.7	1 7	1 2	1
L. U	18	°	10	14	22	27	0.16	0.19	2	4	3	1.5	.	2
B. O	19	♀	3	6	6	15	0 04	0 09	0	0	3	2.4	2-3	?
M. S	7	♂	8	11	10	17	0.10	0.15	6	2	1.5	1 4	1	1
P J	12	♂	1	2	1	2	0	0.01	0	0	.8	1.9	3	2
J P	1	♂	18	22	32	36	0.25	0.29	0	5	3	.4	3	3
L. S	21	♂	7	9	7	9	0.07	0.09	0	0	2.	1	1 2	1 2
B. K	26	♂	18	18	27	29	0.20	0.21	0	11	3	.3	3	3

Caries index was scored according to the DMF system (Klein et al. 1938) In Table I DMFT stands for decayed, missing and filled teeth and DMFS for decayed, missing and filled surfaces. The maximal DMFT number is 28 and the maximal DMFS number is 128. The Westin index is calculated as the ratio of decayed and filled surfaces to 100 selected surfaces of 28 teeth. Missing incisors are evaluated as three surfaces and missing premolars or molars as four surfaces.

The plaque index (Silness & Løe 1964) de... the distribution of soft bacteria-rich ...ris on the teeth.

Scores Criteria

0 No plaque

1 A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface

2 Moderate accumulation of soft deposits within the gingival pocket or on the tooth and gingival pocket, or on the tooth and gingival margin which can be seen with the naked eye

3 Abundance of soft matter within the gingival pocket and or on the tooth and gingival margin

The gingival index (Løe & Silness, 1963) describes the degree of inflammation of the gingiva.

Scores Criteria

0 Absence of inflammation.

1 Mild inflammation—slight change in colour and little change in texture

2 Moderate inflammation—moderate glazing redness, oedema and hypertrophy
Bleeding on pressure.

3 Severe inflammation—marked redness and hypertrophy
Tendency to spontaneous bleeding.
Ulceration.

Both plaque and gingival index can take a maximal value of 3 0 units.

White spot lesions are early caries lesions recognized as a white opacity in the cervical area of the enamel along the gingival margin. It is characterized microscopically as a subsurface lesion under an intact surface They are an indication of high caries activities.

RESULTS

The results from the oral examination are shown in Table I Relatively low values of ca-

ries index are seen. The number of white spot lesions has increased after the operation. In one case (C. P.) 34 such lesions had developed and in another (B. K.) 11 lesions were found one year after operation. Also 5 new lesions (J. P.) indicate an increase in caries activity. In some persons (M. S. and L. U.) some of the white spot lesions noted at the first examination had at the later examination developed into caries cavities. Both before and after the operation large amounts of dental plaque and high values for gingival inflammation were observed.

DISCUSSION

The severe gingivitis of the children in this study corresponds well to the high plaque indices scored. The dental status is on the other hand remarkably good considering the poor oral hygiene. The presence of dental plaque to the extent found here is normally not found in persons of corresponding ages and still only 2 of the test persons (B. J. and M. S.) had caries indices higher than average in their respective age groups. B. J., age 18, thus had a DMFS index of 64, which can be compared with an index number of 40 reported by Andersson (1961) as the mean for 566 18–20-year-old men entering military service. M. S., 7 years old, had a DMFS index of 11, when the mean DMFS index of 1 275 children of this age in the Norrköping study was 5.15 (Sellman & Syrrist, 1968).

The surgical treatment thus might have turned the balance for those whose caries activity earlier was kept low probably mainly due to a diet low in carbohydrates. Three of the cases, C. P., J. P. and B. K., have developed a severe increase in early carious lesions in the form of white spot lesions. Such early lesions, which are found in cases with high caries activity and developed in the cervical regions on the buccal surfaces, are by convention not included in the caries index numbers and are therefore reported separately.

The diet of these institutionalized children is well balanced with regard to calories and nutrients. Fruit like apples, oranges, bananas and pineapples are served between meals and as deserts. Only occasionally—at nine dinners during a 5-week period—are sweetened desserts served. Sweets are given only on Saturdays. The composition of the diet and a probable but not measured, high rate of salivary flow may account for the relatively low caries frequency observed. The flow rates could not be determined due to the lack of capability of cooperation of the children.

Since no changes in diet and only minor changes in prescribed medicine had occurred during the test period, saliva seems to be the factor that can be correlated to the increased caries activity. The increase is seen as higher number of white spot lesions and change from the lesions into carious cavities. The composition of the salivary secretion is obviously changed due to the inactivation of the sublingual gland. The relative importance and influence of the individual secretions in various parts of the oral cavity is also altered after operation. The liquid environment for the incisors is perhaps most affected and in this region the new white spot lesions are found. The composition of the whole secretion has been studied but will be reported elsewhere. It can be mentioned, however, that a decrease in buffer capacity values and an increase of the protein content were found in the test persons one year after operation.

The surgical treatment thus seemed to enhance the susceptibility to caries. A good effect of the operation on the drooling that these children suffer from, would improve the social adjustment for the children. An enhanced caries susceptibility would then not appear as a major contraindication to the surgical treatment. On the other hand it must not be neglected and full cooperation with dentists to make use of optimal caries preventive measures is recommended. The nursing personnel should be trained to assist in the caries prevention program.

ZUSAMMENFASSUNG

Zehn Patienten mit neurologischen Krankheiten und Geifer wurden mit Retroposition der Ausführungsgänge des Gland Submandibulares und Ligatur der Ausführungsgänge des Gland. Sublinguales operiert, um den Geifer zu vermindern. Vorliegende Arbeit beschreibt den Effekt der oben beschriebenen Operation auf die kariogene Aktivität. Untersuchungen des Zustandes der Zähne wurden vor und ein Jahr nach der Operation gemacht. Eine Zunahme der kariogenen Aktivität wurde in einigen Fällen als Vermehrung von oberflächlichem Schmelzkaries oder Übergang von diesem oberflächlichen Schmelzkaries zu Karies registriert. Mit guter oraler Hygiene soll die Gefahr einer Zunahme der kariogenen Aktivität nicht als Kontraindikation der chirurgischen Behandlung gelten.

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COMPTE RENDU
DE LA RÉUNION SCIENTIFIQUE DU

COLLEGIUM
OTO-RHINO-LARYNGOLOGICUM

AMICITIAE SACRUM

BERNE, LE 10-14 SEPTEMBRE, 1972

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NARVAVÄGEN 16, 115 23 STOCKHOLM


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Opening Session September 11 1972

INTRODUCTION

F Escher

Liebe Mitglieder des Collegiums,
meine sehr verehrten Damen und Herren

Chers membres du Collegium,
Mesdames et Messieurs

Dear members of the Collegium,
Ladies and Gentlemen

Mit grosser Dankbarkeit für die Wahl Berns als Tagungsort für das Collegium O.R.L.A.S. 1972 eroffne ich heute die Sitzung. Es freut mich die grosse Zahl von Mitgliedern aus 27 Nationen, die seit Jahren bekannten Freunde und die junge Generation begrüssen zu dürfen ganz besonders herzlich heisse ich die begleitenden Damen und Gäste willkommen. Wir haben versucht, ein gehaltvolles Programm aufzustellen. Besonderer Dank gilt dem Direktor des Inselspitals, Herrn Dr François Kohler und seinem Stab für die grosszügige Gastfreundschaft und die tatkräftige Unterstützung. Über die besondere Stellung des seit über 600 Jahren bestehenden Inselspitals werden Sie von ihm direkt hören.

C'est avec un sentiment profond de gratitude vis-à-vis du Collegium d avoir choisi Berne comme siège pour 1972 que j'ouvre la séance.

Je suis ravi de saluer un grand nombre de membres de 27 nations, les amis connus de puis longtemps et la jeune génération. Je salue tout spécialement les dames et les hôtes. Nous avons essayé de vous offrir un programme intéressant. Je remercie tout spécialement le directeur de l'Hôpital de l Ile et son équipe pour l'hospitalité généreuse et son soutien efficace Il vous donnera tout à l'heure un aperçu sur cet hôpital, fondé il y a plus de 600 ans.

I express gratitude for the choice of Berne as the Meeting place of the Collegium O R.L.A.S. 1972 and declare the session open.

It gives me a great pleasure to welcome the large number of members, from 27 nations, the many well-known faces and the younger generation and I especially welcome the ac companying ladies and guests. We have tried to organize an interesting program and are especially grateful to the Director of the Inselspital and his staff for their generous hospitality and active support. He will tell you personally about the position and activities of the 600-year-old Insel Hospital.

Seit der Gründung des Collegiums 1926 ist es das 3 Mal, dass das Collegium in der Schweiz tagt 1927 bei Fr Nager 1952 bei L. Rüedi je in Zürich und jetzt, 1972, in Bern.

Bern gegründet 1191 von Herzog Berchtold V von Zähringen hat eine ruhmvolle Geschichte und erlangte europäische Bedeu tung in der Konfrontation 1476/77 zu Karl dem Kühnen, Herzog von Burgund. Die Da men werden im Historischen Museum die Schätze der Burgunder Beute bewundern können.

Die auf der Halbinsel der Aare gebaute Stadt hat ihren baulichen Charakter bewahrt. Die Wahrzeichen der Stadt das Münster wurde ab 1421 über fast 100 Jahre Bauzeit und das Rathaus 1406 gebaut In den breiten Gassen entstanden die prachtvollen Brunnen während die heutigen Häuser zum grossen Teil aus der Barockzeit stammen. 1848 wurde Bern die Hauptstadt der Schweiz. Die Universität en stand 1834 hatte aber schon ihre Vorläufe Ich erwähne die grosse geistige Ausstrahlun des Naturwissenschaftlers und Dichters A brecht v Haller im 18 Jahrhundert.

Depuis la fondation du Collegium en 1926 se trouve pour la 3 fois en Suisse, 19 chez Fr Nager à Zurich, 1952 chez L. Rüe à Zurich et maintenant — 20 ans plus tard - à Berne.

Berne fondée en 1191 par le duc Berchtol V de Zähringen a une histoire glorieuse et connu une période d importance européen en 1476/77 lors de la confrontation av Charles le Téméraire duc de Bourgogne. Le dames visiteront les trésors du butin de Bou gogne au Musée historique.

La ville, bâtie sur la presqu'île de l Aare, conservé son caractère médiéval. Les édific significatifs, la cathédrale et la mairie fure commencés au début du 15e siècle Dans le rues larges dès le début on construisit le fameuses fontaines, alors que les maisons ac tuelles avec les arcades sont du baroque E 1848 Berne fut élue comme capitale de l Confédération.

La fondation de l'université date de 1834 il avait auparavant des écoles académiques. J cite le rayonnement spirituel du grand scienti fique et poète A. von Haller au 18e siècle.

Since the foundation of the Collegium in 19 this is the third time that the Congress is bein held in Switzerland In 1927 with Professo Nager in Zurich, in 1952 with Professor Rüe in Zurich and in 1972 in Berne

Berne was founded in 1191 by the Duk Berchtold of Zähringen, has a famous histor and achieved European importance during th confrontation 1476/77 with Charles the Bol Duke of Burgundy The ladies will be able t admire the treasures of the Burgundian wa in the Museum of History

The town of Berne, built on an arm of the River Aare, has kept its architectural charac ter The Cathedral, started in 1421 and com

pleted nearly 100 years later and the town hall, dating from 1406 are the landmarks of the city Beautiful fountains were set up in the wide streets and the majority of the houses date from the baroque period. In 1848 Berne became the capital of Switzerland.

The University was established in 1834 but it had already its precursors. I am referring to the great intellectual emanation of the scientist and poet Albrecht von Haller in the 18th century

Die Oto-Laryngologie ist in Bern in der 5 Generation. Der erste Lehrstuhlinhaber war Prof. Valentin, der Sohn des bekannten Physiologen Valentin. Damit erscheint auch der Name Alfonso Corti verbunden mit Bern. Corti verliess 1848 bei der Revolution Hyrtl in Wien kam nach Bern, arbeitete hier histologisch bei Vater Valentin, bis er dann 1850 zu Koelliker in Würzburg übersiedelte, wo seine grundlegende Arbeit über das Innenohr entstand. F Lüscher Vater E. Lüscher Sohn und mein Lehrer L. Rüedi waren die weiteren Fachvertreter

Heute das Collegium präsidieren zu dürfen ist für mich eine grosse Ehre und Verpflichtung, möge die Tradition der wissenschaftlichen Arbeit auf dem Boden der amicitia sacra blühen und Früchte tragen.

L oto-laryngologie de Berne en est actuellement à sa 5e génération. Le premier titulaire fut le Prof Valentin, le fils du fameux physiologue Valentin Avec celui-ci le nom d Alfonso Corti est lié à Berne. Lors de la révolution 1848 Corti a quitté Hyrtl à Vienne pour s installer chez Valentin à Berne, ou il publia plusieurs travaux histologiques. C'est de Berne qu il se rendit en 1850 chez Koelliker à Würzburg, pour s initier à la recherche de la structure de l oreille interne. Le père F Lüscher le fils E. Lüscher et mon maître L. Rüedi furent les titulaires suivants.

Présider le Collegium aujourd'hui est pour moi une honneur et une obligation C'est mon vœu que la tradition scientifique sur la base de l'amicitia sacra fleurisse et continue de porter des fruits.

The E.N T is in its 5th generation in Berne. The first professor was Prof Valentin, the son of the well-known physiologist Valentin. At the same time the name of A. Corti was also connected with Berne. Corti left Hyrtl in Vienna in 1848 during the Revolution came to Berne, worked here on histology with Valentin senior until he moved to Prof Koelliker in Würzburg in 1850 where his basic studies on the inner ear were published. F Lüscher senior who built the clinic in 1909 E. Lüscher his son, and my teacher L. Rüedi were the next chairmen.

Today the presidency of this Collegium is for me a great honour and responsibility I sincerely hope the tradition of scientific work and deep-rooted friendship will continue to blossom and bear fruits.

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SENSITIZATION AND LOCAL APPLICATION OF ANTIBIOTICS ON THE RESPIRATORY MUCOUS MEMBRANE

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Abstract. Local application of antibiotics to the respiratory mucous membrane in the form of drops and aerosol is more and more often used. Here the question arises of sensitization of the mucosa to the penicillin, being the strongest allergenic remedy. Experimentally we tried with aerosol to provoke the sensitization in rabbits and we observed patients who had received aerosol several times. Laboratory examinations were made in the form of basophil degranulation determinations and compared with the control group. The results are discussed.

During the last 10 years more than 60 000 aerosol inhalations with antibiotics, vasoconstrictors and cortisone have been made in our department. Everyday use of antibiotics in the form of drops applied to the nasal mucosa and the external and middle ear is well known. [illegible] the nasal mucosa is an area of excellent [illegible], the question arises as to the possibility of sensitization of the organism by the aerosol treatment. Clinical experiences have not been able to confirm this supposition which is why we have made an experimental investigation in rabbits and clinical and laboratory examinations in patients after repeated aerosol application of antibiotics. Penicillin was chosen as the most common antibiotic and the one which most frequently causes allergic reactions. Allergic reactions appear in 1 to 15 out of every 1 000 patients treated with penicillin. These reactions can be manifested as erythemo-urticarial reactions all the way to anaphylactoid shock, blood dyscrasias and even death (the fatal reaction is about 1 in 100 000 to 150 000 treatments).

We have been interested, in the first place in the problem whether with frequent local applications of antibiotic, there is a tendency to sensitization of the organism. For our examinations crystal penicillin was chosen which only in this form is used in aerosol.

This work was supported by grant from the Council of Scientific Work of Croatia

MATERIAL AND METHODS

We have divided our work into two parts. The experimental part on rabbits, and the clinical laboratory examination of the patients who received a series of 10 to 15 inhalations. Before this investigation we wanted to ascertain what quantities of penicillin exist in the blood serum with various applications.

	Minutes after application		
	15	60	1[illegible]
1 800 000 I.U. procaine penicillin intramuscularly	4.050	1.640	[illegible]
2 100 000 I.U. benzyl penicillin intramuscularly	1.96	3.420	[illegible]
3 100 000 I.U. with a tampon on the nasal mucosa	0.[illegible]5	0.066	[illegible]
4 100 000 I.U. of penicillin into the maxillary sinus	0.12	0.290	[illegible]
5 Inhalation of 100 000 I.U. of benzyl penicillin	0.0[illegible]3	0.056	[illegible]

Experiments in animals

In the experimental part we used 3 groups of rabbits. In the first group we used 4 rabbits and gave them daily for 10 days, 200 000 I.U.

Table I *Results of indirect test of degranulation of basophil granulocytes (ITDBG) and the test of blastic transformation of lymphocytes (TTL) in the culture before and after inhalation of penicillin*

	1st day								14th day								21st day							
	ITDBG				TTL				ITDBG				TTL				ITDBG				TTL			
	P		C		P		C		P		C		P		C		P		C		P		C	
Sex	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p
M	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0
F	33	0	12	0	33	0	12	0	13	0	12	0	13	0	12	0	13	0	12	0	13	0	12	0
Total	50	0	40	0	50	0	40	0	30	0	40	0	30	0	40	0	30	0	40	0	20	0	40	0

P patients, C, control M, males F females, n, normal p, pathological.

of aerosol penicillin. After 14 days the allergological tests for penicillin remained negative (intradermal, provocative with aerosol, and serological hemagglutinations according to Boyd). In the second group we used 18 rabbits which were given, preliminarily intramuscular crystal penicillin + procaine penicillin with complete Freund adjuvant (2 c.c.) After 3 weeks the tests for penicillin remained negative, including the aerosol. In the third group we infected 4 rabbits with the virus of equine influenza intranasally and intravenously After that, for 10 days, we applied the penicillin aerosol.

The agglutination test in rabbit serum for the equine influenza virus was, after 14 days, positive in the ratio of 1 64 The allergological tests for the penicillin remained negative in all 4 rabbits. Thus we were not able, with 26 rabbits, to provoke an allergic reaction by applying aerosol penicillin, not even with the preliminary intramuscular application and by addition of Freund's adjuvant and the provoked virus infection.

Investigations in patients

We performed the laboratory-clinical investigation with 50 patients, who received penicillin inhalations, and as a control group we took 20 patients without inhalations or with inhalations with a physiological solution only

In all investigated cases, including the controls, the absolute number of basophil and eosinophil granulocytes in the peripheral blood have been determined, and ITDBG (indirect test for degranulation of basophil granulocytes) and TTL (test for lymphocyte transformation) were performed before inhalation of the antibiotic had begun. Absolute numbers of eosinophil and basophil granulocytes were determined also after 7 and 14 days, and ITDBG and TTL 14 and 21 days after inhalation. All these examinations and tests were negative in all cases (Tables I, II)

During this time clinical symptomatology was also negative in not a single person were clinical symptoms noticed which might point to the possibility of an allergic reaction to penicillin.

There was no difference in the number of eosinophils before or after inhalation (Tables III IV). In the repeated series of inhalations, after 1 to 11 months, in 100 cases there were no reactions (Table V).

The number of basophil granulocytes was determined according to *Moore & James* (1953) and that of eosinophil granulocytes by the method of Wintrobe (1961) As normal values we took for basophil granulocytes 15 to 50 cells per cubic millimetre and for eosinophil granulocytes 150 to 300 cells per cubic millimetre. We performed ITDBG according to Shelley with certain slight modifications which do not influence the result of the test (Šoltić & Brnobić, 1966) The test was found negative when the percentage of the damaged

Table II *Absolute number of basophil and eosinophil granulocytes in the peripheral blood before an after inhalation of penicillin*

	1st day								14th day								21st day							
	Basophils				Eosinophils				Basophils				Eosinophils				Basophils				Eosinophils			
	P		C		P		C		P		C		P		C		P		C		P		C	
Sex	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p
M	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0	17	0	[illegible]	[illegible]
F	33	0	12	0	33	0	12	0	13	0	12	0	13	0	1	0	13	0	1	0	13	0	[illegible]	[illegible]
Total	50	0	40	0	50	0	40	0	30	0	40	0	30	0	40	0	30	0	40	0	30	0	40	[illegible]

P patients C control M males, F females; n, normal p, pathological.

cells was less than 25% indefinite when the percentage of the damaged cells was between 25 and 30% and positive when the percentage of the changed basophil granulocytes was 30% or more. We performed TTL by the method of Coulson & Chalmers (1964) slightly modified by Chieregato & Faldarini (1966) In all cases we used the double control. the culture without the addition of antigens and the culture to which we added phytohemagglutinin (Bacto-phytohemagglutinin P Difco Laboratories, Detroit). The culture was estimated positive when in a complete culture (the culture with antigen) stimulation of lymphocytes [illegible]rred (3 or more in the sense of blastic [illegible]ormation), and in the control culture (the one to which no antigen was added) there was no stimulation and when PHA was added there was a pronounced blastic transformation of lymphocytes (40 or more)

DISCUSSION

Penicillin has been studied more extensively than any other antibiotic, but the manner in which it sensitizes is still the matter of lively debate and the semisynthetic penicillins have added a new dimension of antigenicity to the antigenic potential of the older compounds. In the centre penicillin is transformed into penicillemic acid which combines with tissue and yields the antigen penicilloyl protein. This is perhaps the most significant but n[illegible] the only cause for the antigenicity of penicilli[illegible]

Very small quantities of penicillin whic[illegible] are resorbed with aerosol give a far small[illegible] possibility for the formation of penicillo[illegible] protein and, consequently for the possibili[illegible] of the sensitization of the organism. Howeve[illegible] in this procedure relatively larger quantiti[illegible] of penicillin stay on the surface of the nas[illegible] mucosa. According to our measurements th[illegible] amount to 35 to 100 I U per cm^2 of th[illegible] surface which facilitates the action upon th[illegible] mucosa itself We think therefore that i[illegible] halations cannot have any effect on those in[illegible] fections whose localization is deeper in th[illegible] mucosa than a mere superficial inflammator[illegible] reaction, where there is no systematic reactio[illegible] of the organism to such an infection.

Our second conclusion is that by applyin[illegible] aerosol we do not cause a greater likelihoo[illegible] of the sensitization of the organism to a def[illegible]nite antibiotic than the innate liability of th[illegible] organism to such an allergic reaction.

Table III *Eosinophiles in nasal smears before a[illegible] after inhalation of penicillin*

	Negative	Positive	Not taken	Total
Before inhalation	39	5	6	50
After inhalation	38	2	10	50

Table IV *Eosinophils in nasal smears from Control group during 14 day period*

	Negative	Positive	Not taken	Total
1st day	20	1	0	21
14th day	16	1	4	21

RÉSUMÉ

L'application locale des antibiotics sur la membrane muqueuse respiratoire en forme des gouttes et aérosol s'emploi de plus en plus. Il se pose la question de la sensibilisation de la membrane muqueuse le plus souvent à la pénicilline comme le moyen allergique le plus fort. Expérimentalement, nous avons essayé de provoquer la sensibilisation à l'aérosol sur les lapins, nous avons observé les patients qui recevaient l'aérosol plusieurs fois. En même temps nous avons fait les examens en laboratoires dans forme de dégranulation basophile et nous avons fait la comparaison avec le groupe contrôle. Les résultats sont présentés.

ZUSAMMENFASSUNG

Die lokale Applikation von Antibiotika auf die Respirationsschleimhaut in Form von Tropfen und Aerosol wird immer mehr angewendet. Dabei stellt sich die Frage der Sensibilisation der Schleimhaut besonders auf Penicillin, den stärksten allergenen Mittel, der Wir versuchten auf den Kaninchen die Sensibilisation experimentell auszuführen und beobachteten auch die Patienten bei denen der Aerosol mehrfach verwendet wurde. Dabei waren die laboratorischen Untersuchungen in Form der basophylen Degranulation durchgeführt und mit denen der Kontrollgruppe in Vergleich gestellt. Die Resultate werden aufgeführt.

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DISCUSSION

H H Naumann: Die Fragestellung von Herrn Krajina ist vom Prinzip her sehr aktuell, denn es geht ja darum, ob wir mit einer intranasalen Medikation Arzneimittelallergie induzieren können oder nicht. Nur glaube ich, dass die gewählte Testsubstanz zur Beantwortung dieser Frage kaum geeignet ist. Die Penicilline sind niedermolekular und als echte wässerige Lösung gehen sie praktisch mit der Geschwindigkeit einer intravenösen Injektion von der Schleimhautoberfläche der Nase in die Blutbahn über. Mein Mitarbeiter Dr Mdazel konnte jüngst sowohl isotopentechnisch als auch autoradiographisch zeigen, dass bei derartigen Substanzen die Resorptionsleistung der Nasenschleimhaut sehr deutlich an die Epithelzellen gebunden ist, während überraschenderweise die Lamina propria, welche für immunologische Vorgänge in erster Linie zuständig wäre, bei niedermolekularer wässerigen Lösungen keine Speicherungsphänomene zeigt. Die Passage derartigen Flüssigkeiten geht direkt vom Epithel vorwiegend interzellulär zu terminalen Strombahn, d. h. ins Blut. Damit entfällt theoretisch die Wahrscheinlichkeit, mit Penicillin in wässeriger Lösung an der Nasenschleimhaut immunologische Reaktionen erzielen zu können. Deshalb meine Frage an Herrn Krajina: Haben Sie auch andere, höhermolekulare bzw kolloidale Medikamente verwendet oder Wirkstoffe, die eventuell an ein Protein oder Proteid gekoppelt waren?

Table V *Repeated inhalations: Second series (91 patients) Third series (9 patients)*

	Period (in months) between first and second, or second and third series of inhalations													
	½	1	1½	2	2½	3	3½	4	5	6	7	8	10	11
Patients	24	8	10	5	10	5	3	6	4	4	9	4	7	1

Table II *Absolute number of basophil and eosinophil granulocytes in the peripheral blood before and after inhalation of penicillin*

	1st day								14th day								21st day							
	Basophils				Eosinophils				Basophils				Eosinophils				Basophils				Eosinophils			
	P		C		P		C		P		C		P		C		P		C		P		C	
Sex	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p	n	p
M	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0	17	0	28	0
F	33	0	12	0	33	0	12	0	13	0	12	0	13	0	12	0	13	0	12	0	13	0	12	0
Total	50	0	40	0	50	0	40	0	30	0	40	0	30	0	40	0	30	0	40	0	30	0	40	0

P patients C control M males, F females n, normal p, pathological.

cells was less than 25% indefinite when the percentage of the damaged cells was between 25 and 30% and positive when the percentage of the changed basophil granulocytes was 30% or more. We performed TTL by the method of Coulson & Chalmers (1964) slightly modified by Chieregato & Faldarini (1966) In all cases we used the double control the culture without the addition of antigens and the culture to which we added phytohemagglutinin (Bacto-phytohemagglutinin P Difco Laboratories, Detroit) The culture was estimated positive when in a complete culture (the culture with antigen) stimulation of lymphocytes occurred (3 or more in the sense of blastic transformation), and in the control culture (the one to which no antigen was added) there was no stimulation and when PHA was added there was a pronounced blastic transformation of lymphocytes (40 or more)

DISCUSSION

Penicillin has been studied more extensively than any other antibiotic but the manner in which it sensitizes is still the matter of lively debate and the semisynthetic penicillins have added a new dimension of antigenicity to the antigenic potential of the older compounds. In the centre penicillin is transformed into penicillenic acid which combines with tissue and yields the antigen, penicilloyl protein This is perhaps the most significant but not the only cause for the antigenicity of penicillin.

Very small quantities of penicillin which are resorbed with aerosol give a far smaller possibility for the formation of penicilloyl protein and, consequently for the possibility of the sensitization of the organism. However in this procedure relatively larger quantities of penicillin stay on the surface of the nasal mucosa. According to our measurements they amount to 35 to 100 I.U per cm² of the surface which facilitates the action upon the mucosa itself We think therefore, that inhalations cannot have any effect on those infections whose localization is deeper in the mucosa than a mere superficial inflammatory reaction where there is no systematic reaction of the organism to such an infection.

Our second conclusion is that by applying aerosol, we do not cause a greater likelihood of the sensitization of the organism to a definite antibiotic than the innate liability of the organism to such an allergic reaction.

Table III *Eosinophiles in nasal smears before and after inhalation of penicillin*

	Negative	Positive	Not taken	Total
Before inhalation	39	5	6	50
After inhalation	38	[illegible]	10	50

Table IV *Eosinophils in nasal smears from Control group during 14 day period*

	Negative	Positive	Not taken	Total
1st day	20	1	0	21
14th day	16	1	4	21

RÉSUMÉ

L'application locale des antibiotics sur la membrane muqueuse respiratoire en forme des gouttes et aérosol s'emploi de plus en plus. Il se pose la question de la sensibilisation de la membrane muqueuse le plus souvent à la penicilline comme le moyen allergique le plus fort. Expérimentalement, nous avons essayé de provoquer la sensibilisation à l'aérosol sur les lapins, nous avons observé les patients qui reçevaient l'aérosol plusieurs fois. En même temps nous avons fait les examens en laboratoires dans forme de dégranulation basophile et nous avons fait la comparaison avec le groupe contrôle. Les résultats sont présentés.

ZUSAMMENFASSUNG

Die lokale Applikation von Antibiotika auf die Respirationsschleimhaut in Form von Tropfen und Aerosol wird immer mehr angewendet. Dabei stellt sich die Frage der Sensibilisation der Schleimhaut besonders auf Penicillin, den starksten allergenen Mittel, der Wir ersuchten auf den Kaninchen die Sensibilisation experimentell auszuführen und beobachteten auch die Patienten bei denen der Aerosol mehrfach verwendet wurde. Dabei waren die laboratorischen Untersuchungen in Form der basophylien Degranulation durchgeführt und mit denen der Kontrollgruppe in Vergleich gestellt. Die Resultate werden aufgeführt.

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DISCUSSION

H. H. Naumann. Die Fragestellung von Herrn Krajina ist vom Prinzip her sehr aktuell, denn es geht ja darum, ob wir mit einer intranasalen Medikation Arzneimittelallergie induzieren können oder nicht. Nur glaube ich, dass die gewählte Testsubstanz zur Beantwortung dieser Frage kaum geeignet ist. Die Penicilline sind niedermolekular und als echte wässerige Lösung gehen sie praktisch mit der Geschwindigkeit einer intravenösen Injektion von der Schleimhautoberfläche der Nase in die Blutbahn über. Mein Mitarbeiter Dr. Munzel konnte jüngst sowohl isotopentechnisch als auch autoradiographisch zeigen, dass bei derartigen Substanzen die Resorptionsleistung der Nasenschleimhaut sehr deutlich an die Epithelzellen gebunden ist während überraschenderweise die Lamina propria, welche für immunologische Vorgänge in erster Linie zuständig wäre, bei niedermolekularer wässerigen Lösungen keine Speicherungsphänomene zeigt. Die Passage derartigen Flüssigkeiten geht direkt vom Epithel vorwiegend interzellulär zu terminalen Strombahn, d. h. ins Blut. Damit entfällt theoretisch die Wahrscheinlichkeit, mit Penicillin in wässriger Lösung an der Nasenschleimhaut immunologische Reaktionen erzielen zu können. Deshalb meine Frage an Herrn Krajina: Haben Sie auch andere, hochermolekulare bzw. kolloidale Medikamente verwendet oder Wirkstoffe, die eventuell an ein Protein oder Proteid gekoppelt waren?

Table V *Repeated inhalations: Second series (91 patients), Third series (9 patients)*

	Period (in months) between first and second, or second and third series of inhalations													
	½	1	1½	2	2½	3	3½	4	5	6	7	8	10	11
Patients	24	8	10	5	10	5	3	6	4	4	9	4	7	1

T. Lerpaard. It is my sincere conviction that in 99 out of a 100 times local application of antibiotics is useful only to influence our normal, useful mixture of micro-organisms in the nose and throat and which, besides possible sensitization, is resulting only in destroying the ecology of the micro-organisms.

H. C. Andersen. I think it is very important that Mr Krajina has shown us that local application of penicillin in the nose is not dangerous, but I think he owes us the proof that such application has any therapeutic effect.

Z. Krajina (Reply): Our intention was to prove that it is possible to sensitize the organism more effectively through the application of aerosol penicillin. We wer surprised at the small quantity of penicillin in th blood after the inhalation. Perhaps that was du t the scattering of penicillin over the respiratory muco after the application of the aerosol. We used in ou work only antibiotics combined with vasoconstrict and cortisone and I have not tried any substances w high molecular weight. About the value of aeros in clinical practice: only superficial infection of th respiratory mucosa can be influenced by aerosol otherwise it is necessary to use antibiotics systemically or in combination with the aerosol.

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MORPHOLOGISCHE UNTERSUCHUNGEN ZUR RETIKULIERUNG DES TONSILLENEPITHELS

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Abstrakt Im Tierversuch läßt sich die Retikulierung des Kryptenepithels durch Gaben von Cortison und Desoxycorticosteron variieren. Das Ausmaß der retikulierten Epithelabschnitte geht postnatal mit der Ausbildung der Sekundärfollikel parallel. Die Retikulierung wird als ein physiologischer Vorgang angesehen. Elektronenmikroskopisch stellt sich der Retikulierungsvorgang wie folgt dar: zunächst gelangen Lymphocyten zwischen zwei Epithelzellen durch die Basalmembran in tiefe Epithelschichten. Weitere Zellen dringen durch die so entstandenen Lücken in das Epithel ein, wo sie dann zwischen fein ausgezogenen Fortsätzen der Epithelzellen in einem Ödemsee liegen. In den mittleren und oberen Epithelschichten finden sich ferner Lymphoblasten in Teilung. Gelegentlich beobachtet man Lymphocyten über intakter Basalmembran. Beim Menschen wird das Retikulierungsbild von entzündlichen Veränderungen überlagert. Die morphologischen Befunde werden in Beziehung zur Tonsillenfunktion gesetzt. Auf das Vorkommen von Langerhans-Zellen im Epithel der menschlichen Gaumenmandel wird eingegangen.

Neuere Ergebnisse über die immunologische Funktion der Tonsilla palatina lassen es als gesichert erscheinen, daß dieses lymphoepitheliale Organ eine wesentliche Rolle bei der Immunisierung des gesamten Organismus spielt (Naumann 1957 Meyer zum Gottesberge & Koburg, 1967 Koburg, 1970) Diese Erkenntnisse veranlaßten uns, auch elektronenmikroskopisch das Epithel der Gaumenmandel unter besonderer Berücksichtigung seiner Retikulierung zu analysieren. Im Rahmen dieser Untersuchungen fanden wir erstmals Langerhans-Zellen im Epithel der Gaumenmandel des Menschen

Während unsere Kenntnisse über die Ultrastruktur des retikulierten Kryptenepithels, das für die spezifische Tonsillenfunktion im Rahmen immunologischer Vorgänge von so großer Bedeutung ist, nur spärlich sind, finden sich lichtmikroskopisch zahlreiche Untersuchungen (Stöhr 1882, 1884 Dietrich 1923 Watzka, 1932, Schwarz, 1953 Kelemen, 1954 Boenninghaus, 1955 Yamaguchi, 1960· Fioretti, 1961 Grau, 1965) Die Schwierigkeiten bei der Deutung dieses Vorganges waren vor allem darin begründet, daß fast immer operativ entfernte Tonsillen von Menschen verwendet wurden, bei denen das physiologische Retikulierungsbild durch pathologische Veränderungen bei chronischer Tonsillitis überlagert war

Den Retikulierungsvorgang am Kryptenepithel der Tonsilla palatina versuchten wir daher an nicht entzündlich veränderten Tonsillen weiter abzuklären. Zu diesen Untersuchungen bot sich uns die Kaninchentonsille an an der wir schon früher bei tierexperimentellen Studien mit Nebennierenrindenhormonen das Ausmaß der Retikulierung des Tonsillenepithels modifizieren konnten (Falk & Schätzle, 1962 Schätzle & Falk, 1962)

MATERIAL UND METHODIK

1 *Tierexperimentelle Untersuchungen zum Retikulierungsvorgang am Kryptenepithel der Tonsilla palatina nach Injektion von Cortison Methylprednisolon und Desoxycorticosteron (DOCA)*:

a) *Cortison.* 6 Kaninchen (Rasse „Grau Silber" 31 Tage alt) erhielten an 6 aufeinanderfolgenden Tagen je 40 mg/kg Körpergewicht subcutan. 2 Tage danach Dekapitation. 5 Kontrolltiere.



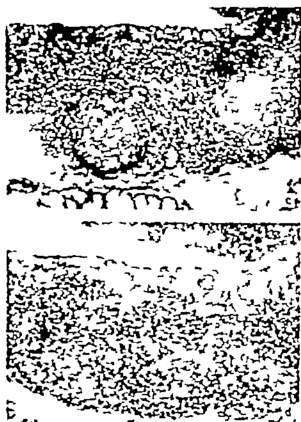


Abb. 1. (*a*) Kontrolltier: Deutliche Retikulierung über den Sekundärfollikeln. (*b*) 6 × 40 mg Cortison. Atrophie des lymphatischen Gewebes. Sporadisch retikuliertes Kryptenepithel. (*c*) 6 × 40 mg Cortison und 4 × 15 mg DOCA. Cortisonbedingte Atrophie des lymphatischen Gewebes aufgehoben. Kräftige Retikulierung. (*d*) 4 × 15 mg DOCA. Epithel über weite Strecken durchgehend retikuliert. Dicht nebeneinander liegende Sekundärfollikel mit Polkappe. 70×

b) *Methylprednisolon.* 9 Kaninchen (Rasse „Grau Silber", 10 Monate – 2 Jahre alt). 6 × 20 mg/kg Körpergewicht. 7 Kontrolltiere. Töten der Tiere 2 Tage nach der letzten Injektion durch Einspritzen von Chloroform in die Nasenhöhle.

c) *Desoxycorticosteron.* 14 Kaninchen (Rasse „Grau-Silber", 28–50 Tage alt) wurden 4 × 15 mg/kg Körpergewicht subcutan injiziert. Dekapitation 2 Tage nach der letzten Injektion. 7 Kontrolltiere.

d) *Cortison und Desoxycorticosteron.* 1? Kaninchen (Rasse „Deutscher Widder", 10 Monate alt) wurden 6 × 40 mg/kg Körpergewicht Cortison verabreicht und nach einer Pause von 2 Tagen 4 × 15 mg/kg DOCA. 10 Kontrolltiere (unbehandelt, 6 × 40 mg Cortison, 4 × 15 mg DOCA). Töten der Tiere 2 Tage nach der letzten Injektion.

2. *Tonsillen von 12 Kindern*, die wegen hyperplastischer chronischer Tonsillitis tonsillektomiert wurden.

3. *Untersuchungstechnik*

a) *Lichtmikroskopie*. Fixation in 10%igem neutralem Formalin, Paraffineinbettung. Färbungen: HE, Goldner, Aldehydthionin nach Specht (1970), Perjodsäure-Bisulfit-Aldehydthionin (PBA-Reaktion) nach Specht, PBA-Methode nach Vorbehandlung mit Diastase, Toluidinblau (pH 3–4).

b) *Elektronenmikroskopie*[1]. Immersionsfixation in 6,25%igem eisgekühltem Glutaraldehyd in Sörensen-Phosphatpuffer (pH 7,4) über 1? Stunden. Zweistündige Nachfixation in 1%iger Osmiumsäure in Veronal-Acetat-Puffer (pH 7,4) mit Zusatz von 4,5% Saccharose (Caul-

[1] Herrn Dr. Mäusle (Pathologisches Institut) danken wir für die Unterstützungen bei den elektronenmikroskopischen Untersuchungen.



Abb. 2 Erwachsenes Kontrolltier. PBA-Färbung nach Specht. Basalmembran unter dem retikulierten Epithel unterbrochen. 260

field, 1957). Nach Araldideinbettung wurden die Ultradünnschnitte (Ultramikrotom Om U 2, Fa. Reichert) mit Uranylacetat (Watson, 1958) und Bleicitrat (Reynolds, 1963) kontrastiert. Auswertung mit dem Zeiss EM 9 S2. Kontrollschnittfärbungen: Methylenblau (Unna), Movat Versilberung.

4. Zum Nachweis der *Langerhans-Zellen* im Epithel der menschlichen Gaumenmandel kamen 22 Tonsillenpaare, die wegen chronischer Tonsillitis ausgeschält wurden, zur Untersuchung.

a) *Lichtmikroskopische Untersuchungen.* HE und Melaninfärbung nach Fixation des Gewebes in neutralem 10%igem Formalin. Osmium-Zinkjodid-Methode nach Maillet (1959). Semidünnschnittfärbung mit Methylenblau (Unna).

b) *Elektronenmikroskopie.* Fixation der aufgeschnittenen Tonsillen über 12 Stunden in 6,25%igem eisgekühltem Glutaraldehyd in Sörensen-Phosphatpuffer (pH 7,4). Gezielte Entnahme von Oberflächen- und Kryptenepithel. Weiterverarbeitung wie unter 3b beschrieben.

ERGEBNISSE

Lichtmikroskopische Befunde an der Kaninchentonsille

Kontrolltiere

Die Tonsilla palatina besitzt meist nur eine zentral gelegene Krypte. Bei den jungen Tieren sind die extrafollikulär gelegenen Lymphocyten mäßig dicht angeordnet. Die Sekundärfollikel liegen nahe beieinander. Die Retikulierung des Epithels ist stärker über den Sekundärfollikeln ausgeprägt, geht aber auch auf die interfollikulären Areale des Epithels über.

Bei den erwachsenen Kontrolltieren sind die zahlreichen Sekundärfollikel mit Lymphocytenkappen und hellen Zentren ebenso gut ausgebildet wie das extrafollikuläre lymphatische Gewebe. Im Gegensatz zu den Jungtieren ist das Kryptenepithel höher. Die Retikulierung ist nur auf die Zone über den Kopf







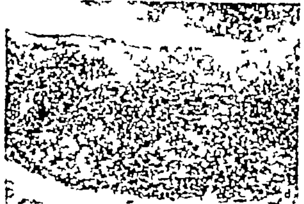


Abb 1 (a) Kontrolltier Deutliche Retikulierung über den Sekundärfollikeln. (b) 6 40 mg Cortison Atrophie des lymphatischen Gewebes. Sporadisch retikuliertes Kryptenepithel. (c) 6 40 mg Cortison und 4 15 mg DOCA. Cortisonbedingte Atrophie des lymphatischen Gewebes aufgehoben. Kräftige Retikulierung. (d) 4 15 mg DOCA. Epithel über weite Strecken durchgehend retikuliert. Dicht nebeneinander liegende Sekundärfollikel mit Polkappe 70

b) *Methylprednisolon* 9 Kaninchen (Rasse „Grau Silber" 10 Monate – 2 Jahre alt). 6 20 mg/kg Körpergewicht. 7 Kontrolltiere. Töten der Tiere 2 Tage nach der letzten Injektion durch Einspritzen von Chloroform in die Nasenhöhle.

c) *Desoxycorticosteron.* 14 Kaninchen (Rasse „Grau Silber" 28–50 Tage alt) wurden 4× 15 mg/kg Körpergewicht subcutan injiziert. Dekapitation 2 Tage nach der letzten Injektion 7 Kontrolltiere.

d) *Cortison und Desoxycorticosteron.* 12 Kaninchen (Rasse „Deutscher Widder 10 Monate alt) wurden 6 × 40 mg/kg Körpergewicht Cortison verabreicht und nach einer Pause von 2 Tagen 4 × 15 mg/kg DOCA. 10 Kontrolltiere (unbehandelt 6 × 40 mg Cortison, 4 × 15 mg DOCA) Töten der Tiere 2 Tage nach der letzten Injektion.

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3 *Untersuchungstechnik*

a) *Lichtmikroskopie* Fixation in 10 %igem neutralem Formalin Paraffineinbettung. Färbungen HE, Goldner Aldehydthionin nach Specht (1970), Perjodsäure Bisulfit Aldehydthionin (PBA Reaktion) nach Specht, PBA Methode nach Vorbehandlung mit Diastase. *Toluidinblau (pH 3–4)*

b) *Elektronenmikroskopie*[1] Immersionsfixation in 6,25 %igem eisgekühltem Glutaraldehyd in Sörensen-Phosphatpuffer (pH 7 4) über 12 Stunden. Zweistündige Nachfixation in 1 %iger Osmiumsäure in Veronal-Acetat Puffer (pH 7 4) mit Zusatz von 4,5 % Saccharose (Caul-

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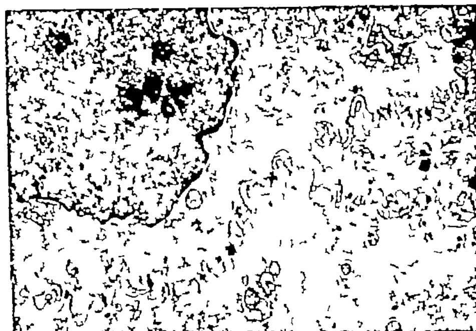


Abb. 6. Intermediärschicht. Kern abgerundet. Tonofibrillen im Cytoplasma. 10 000.

Das retikulierte Kryptenepithel

Über den Sekundärfollikeln treten mehr und mehr Lymphocyten, Plasmazellen und Makrophagen unter der Basalmembran auf und drängen hier die Kollagenfasern auseinander. Einzelne Zellen stülpen die Basalmembran ein, so daß Pseudopapillen entstehen, die licht mikroskopisch dem Bild der gewellten Basalmembran entsprechen (Abb. 8). Demgegenüber sind die echten Papillen gut abgrenzbar, da sie eine zentrale Kapillare enthalten, deren Endothelzellen an der Außenseite eine eigene Basalmembran besitzen und von einem schmalen Stroma umgeben sind (Abb. 9). Ist das Gefäß im Epithel quergetroffen, dann erkennt man die echte Papille an dem schmalen Bindegewebsmantel mit Kollagenfasern, die das Gefäß umgeben. Kapillaren ohne Bindegewebsmantel kommen im Epithel nicht vor.

Die Basalmembran ist an vielen Stellen in unterschiedlicher Breite unterbrochen (Abb. 10). Durch diese Lücken gelangen Rundzellen zwischen die basalen Epithelien, die auseinandergedrängt werden. Die Epithelien werden schmaler und stark ausgezogen, so daß ein weites Maschenwerk vorliegt (Abb. 11). Zwischen diesen schmal ausgezogenen zusammenhängenden Epithelfortsätzen liegen die eingeschleusten Zellen in einem Ödemsee. Bei den Zellen handelt es sich um Lymphocyten, Plasmazellen und Makrophagen. In den beiden oberen Zellschichten liegen auch Lymphoblasten, von denen sich einzelne in Teilung befinden. Plasmazellen sind selten vorhanden. Hat die Retikulierung alle Epithelschichten erfaßt, so ist die oberste Epithelzellreihe schmal ausgezogen und vorgebuckelt (Abb. 12).

Das Retikulierungsbild der kindlichen Gaumenmandel

Lichtmikroskopisch lag immer eine unspezifische chronische Kryptentonsillitis vor. Die Retikulierung war über den Sekundärfollikeln am stärksten ausgeprägt.

Elektronenmikroskopisch entsprechen der Epithelaufbau und das Retikulierungsbild den Befunden beim Kaninchen. Quantitativ ist der Umfang der Retikulierung jedoch bedeutend



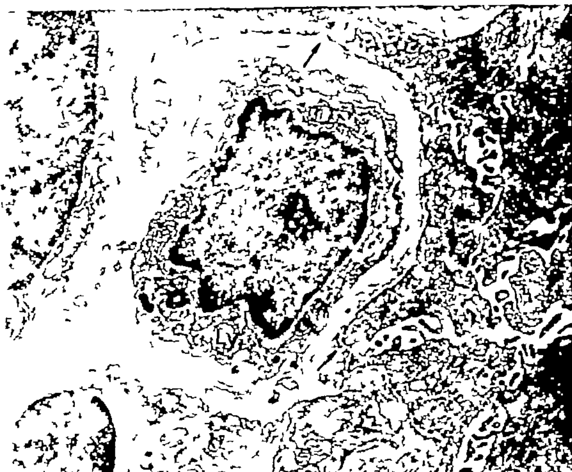
Abb 7 Stratum superficiale. Zellen abgeflacht. Verzahnung der Zellen durch kurze Fortsätze, die auch zum Kryptenlumen hin vorhanden sind. ×4 000.

stärker Dabei ist die Basalmembran oft nur noch bruchstückhaft vorhanden. Wenige ausgezogene Epithelzellen liegen zwischen massenhaften Rundzellen Vermehrt kommen Plasmazellen vor sie umsäumen häufig breit die apillaren innerhalb der Papillen (Abb 13) Jcht selten finden sich neutrophile Granulo-ten im retikulierten Epithel. Auch Lymphoblasten in Teilung kommen vor

Elektronenmikroskopischer Nachweis von Langerhans-Zellen im Oberflächen- und Kryptenepithel der menschlichen Gaumenmandel

Im Osmium-Zinkjodid-Präparat sieht man im Oberflächen- und Kryptenepithel suprabasal gelegene tiefschwarze dendritenartig verzweigte Zellen, die dicht beieinanderliegen und mit ihren Ausläufern zu anastomosieren scheinen (Abb 14). Sie können mit den Langerhans-Zellen der Epidermis verglichen werden. Nur wenige dieser Zellen liegen im Stratum basale, aber keine im darunter liegenden subepithelialen Gewebe. Die Melaninfärbung ist negativ Im methylenblaugefärbten Kontrollschnitt haben diese Zellen ein helles Cytoplasma und einen stark eingebuchteten Kern.

Elektronenmikroskopisch besitzen diese Zellen ein gering elektronendichtes Cytoplasma (Abb 15). Sie sind nicht durch Desmosomen mit den benachbarten Zellen verbunden. Der Kern hat tiefe Einbuchtungen, ein lockeres Chromatingerüst und einen deutlichen Nukleolus. Im hellen Cytoplasma finden sich [illegible]-liche Mitochondrien vom Crista Typ. Der Golgi-Apparat und das endoplasmatische Retikulum sind unauffällig. Lysosomen und Zentriolen kommen ebenfalls vor Zwischen Golgi-Feld und der Zellmembran sowie meist nur auf eine Zellhälfte beschränkt liegen stäbchenförmige, seltener auch tennisschlägerartige Strukturen und rasterartige Areale (Abb. 16) Die stäbchenförmigen Langerhans-Zell-Granula besitzen eine deutliche Querstreifung mit einer Periodik von 90 A. Im Krypten- und Oberflächenepithel wurden die Langerhans-Zellen erstmals in Teilung gesehen. Seltener Lie-



8 Pseudopapille durch Vorbuchtung der in- Basalmembran (→). Lymphocyt (Ly). 11 750.

…ch in den peripheren Zellausläufern kom- …förmig gekrümmte Stäbchen dicht neben- …nander

DISKUSSION

…ie Retikulierung des Epithels wird heute …ist als eine spezifische, physiologisch wesent…he Eigenschaft des Tonsillengewebes und …cht als eine Antwort auf entzündliche Reize …ngesehen (Stöhr 1884 Berggren & Hellman, …930· Schwarz, 1953 Moser & Braun, 1954 …oretti, 1961 Falk, 1963 Koburg, 1970· …mann, 1970). Dafür spricht auch, daß die …aumenmandeln schon beim 6 Monate alten …oeten retikuliertes Epithel enthalten. Auch …ei unseren jungen Kaninchen waren niemals Zeichen der Entzündung, aber immer retikulierte Epithelabschnitte vorhanden.

Wie schon bekannt, unterscheidet man am nicht retikulierten Epithel elektronenmikroskopisch eine Basalzellschicht, eine Intermediärschicht und eine oberflächliche Schicht (Kato 1964 Nosaka, 1966) Diese Autoren fanden zur Basalzellschicht hin zunehmend weiter werdende Interzellularräume. In optimal fixierten Gewebsschnitten bleibt jedoch die Erweiterung des interzellulären Spaltraumes aus. Da man auch oft perinukleäre Spalträume in den Zellen beobachtet, zwischen denen weite interzelluläre Spalträume liegen, besteht der dringende Verdacht, daß es sich um Schrumpfungsartefakte handelt. Man kann auch nicht



Abb 9 Echte Bindegewebspapille mit Kapillare (C). Basalmembran (→) nicht unterbrochen 5 000

Nosaka zupflichten der annimmt daß die in die basal gelegenen Interzellularräume hinein ragenden Zellfortsätze eine Resorptionsfunktion besitzen denn es fehlen Resorptionsvakuolen und ein gut ausgebildeter lysosomaler Apparat

Da bisher nur lichtmikroskopische Befunde vom retikulierten Epithel vorlagen, wa[illegible]



Abb. 10 Retikulierung. Basalmembran unterbrochen (→). Lymphocyten dringen in das Epithel ein. 4 250

Aussagen über das Verhalten der elektronenmikroskopisch sichtbaren, für den Retikulierungsvorgang wichtigen Basalmembran kaum möglich. Die bisher angewandten Bindegewebsfärbungen stellten neben den Kollagenfasern ...h ungeformte Bindegewebsstrukturen dar ... der Aldehydthionin-Methode nach Specht (1970) wird der Verlauf der Basalmembran deutlicher dargestellt, da die Kollagenfasern nicht angefärbt werden. Mit dieser Methode ... sich die Lage der unmittelbar subepithelial gelegenen oder in den Bindegewebspapillen zum Epithel hin verlaufenden Kapillaren gut beurteilen. Die vieldiskutierte Frage, ob in nicht retikuliertem Epithel Kapillaren vorkommen (Naumann, 1954) oder nicht (Boenninghaus, 1955) und wie diese sich bei der Retikulierung des Epithels verhalten, konnte jedoch nur elektronenmikroskopisch geklärt werden.

Ultrastrukturell kommen nach unseren Befunden *keine Kapillaren* im *nicht retikulierten*



Abb 11 Lymphocyten (*Ly*) in einem Ödemsee zwischen schmal ausgezogenen Fortsätzen der Epithelzellen (*E*). 4 500

Gewebe bei erhaltener Basalmembran vor Die in quer und längs getroffenen Papillen liegenden Kapillaren haben eine eigene unter den Endothelzellen verlaufende Basalmembran und sind von einem Bindegewebsmantel mit Kollagenfasern umgeben Erst daran anschließend liegt die Basalmembran der basalen Epithelzellen. Die Kapillaren sind somit dem extraepithelialen Gewebe zuzuordnen

Die *Kapillaren im retikulierten Epithel* grenzen ebenfalls niemals direkt an die Epithelzellen, wie dies von Drabe & Girschik (1963) behauptet wird sie werden immer von Bindegewebsfasern umgeben Die Basalmembran ist nur zwischen den Epithelzellen unterbrochen d. h daß auch im retikulierten Epithel die Basalzellen stets durch eine Basalmembran gegenüber dem Bindegewebsmantel der Kapillaren abgegrenzt werden Auch der Behauptung von Schwarz (1953), daß am Beginn der Retikulierung von der Papille aus eine Einsprossung von Kapillaren durch die Basalmembran erfolgt können wir nicht zustimmen da wir niemals dort Kapillarsprossen beobachten konnten.

Am Epithel beobachteten wir bei der Retikulierung elektronenmikroskopisch verschiedene Zustandsbilder wellenformig verlaufende Basalmembran Vorhandensein von Bruchstücken oder streckenweises Fehlen der Basalmembran manchmal Intaktsein der Basalmembran trotz ausgeprägter Retikulierung

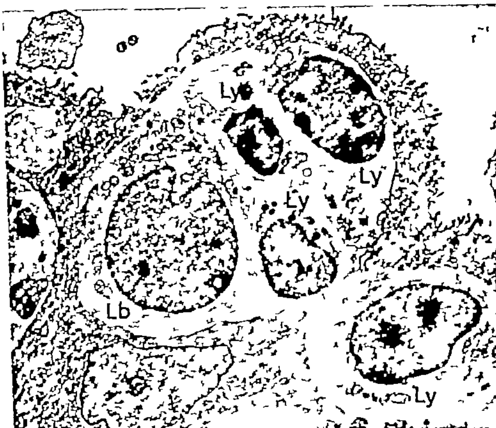


Abb. 12 Lymphocyten (*Ly*) und Lymphoblasten (*Lb*) im Stratum superficiale. 5 000.

Wir schließen aus dem gleichzeitigen Nebeneinander derartiger Bilder auf zeitlich hintereinandergeschaltete, unterschiedlich weit fortgeschrittene Retikulierungsstadien.

Die *Retikulierung* beginnt mit der Wellung der Basalmembran. Meist liegen unter der eingebuchteten Basalmembran Lymphocyten (Pseudopapillen). Dann bricht zwischen den basalen Epithelzellen die Basalmembran auf. Durch die so entstandenen Lücken dringen Lymphocyten in das Epithel ein. Durch das Auseinandergehen der Epithelzellen entstehen breitere Lücken. Lymphocyten und Plasmazellen sowie deren Vorstufen liegen dann in kleinen Gruppen in einem Ödemsee, so daß die Epithelzellen weit auseinandergeschoben, nur durch lang auseinandergezogene Zellfortsätze netzartig miteinander verbunden sind.

Der Ödemsee entsteht nach unserer Meinung durch Flüssigkeitsverschiebung aus dem lymphatischen Parenchym in das Epithel bei unterbrochener Basalmembran. Das epitheliale Maschenwerk erscheint geeignet, die Lymphocyten im Epithel festzuhalten, so daß längere Kontakte mit Antigenen ermöglicht werden.

Im retikulierten Epithel fanden wir niemals zwischen den Rundzellen Bindegewebsfasern. Nach Aufbruch der Basalmembran war auch niemals ein Kriterium für das Vorwachsen der Papillen, noch eine explosionsartige Durchwanderung über den Sekundärfollikeln zu sehen, wobei sich dann lymphatische Zellen und Bindegewebsfasern in das Kryptenlumen entleeren sollen, wie dies Kelemen (1943, 1954) sah.

Bei den tierexperimentellen Untersuchungen



Abb 13 Kindliche Tonsille Quergeschnittene Papille mit Kapillare (*C*), die nur von Plasmazellen (*Pc*) umgeben ist. ×4 500

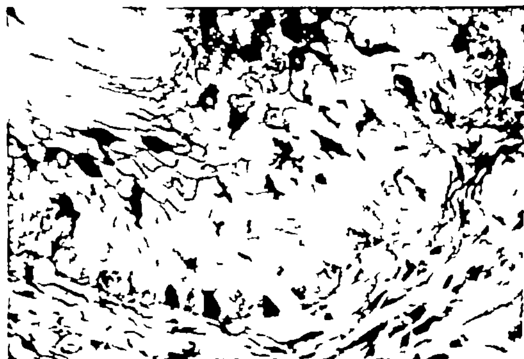


Abb 14 Menschliches Gaumenmandelepithel Osmium-Zinkjodid Methode Suprabasal gelegene Dendriten-Zellen. ×740



Abb. *15* Langerhans-Zelle mit gelapptem Zellkern (N) und hellem Cytoplasma. Mehrere stäbchenförmige Strukturen (→) zwischen Golgi-Feld (*G*) und Zellmembran. Desmosomen fehlen. 11 000.

mit Nebennierenrindenhormonen konnten wir Ausmaß der Retikulierung modifizieren, daß eine Entzündung mit im Spiel war. Wir konnten so den Retikulierungsvorgang unverfälscht darstellen. Die Versuche mit DOCA zeigten auch, daß die Stärke der Retikulierung parallel zur Ausbildung der Sekundärfollikel verläuft. Das Retikulierungsbild war

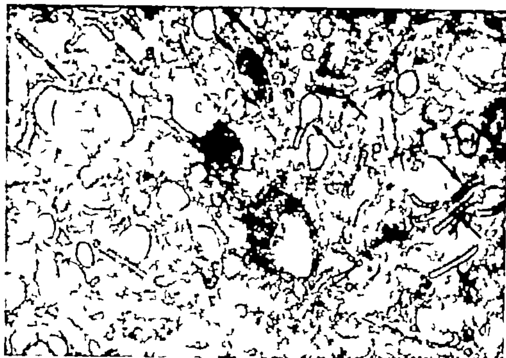


Abb 16 Langerhans-Zell-Granula. Tennisschläger artige und stäbchenförmige Anschnitte sowie raster artige Areale (→). ×4 500

aber gleich Die Retikulierung stellt sich an den Tonsillen von Mensch und Kaninchen gleich dar Bei den chronisch entzündeten menschlichen Tonsillen wird jedoch das Bild von entzündlichen Reaktionen überlagert.

Unsere Ergebnisse am retikulierten Epithel er Tonsille lassen sich mit den neueren Ergeb- ssen der immunologischen Funktion der Ton sille in Beziehung setzen. Das retikulierte Epi thel ist ein wichtiges Glied in einem mitein ander verbundenen Immunsystem (Keimzen trum, Lymphocytenkappe subepitheliale Zone retikuliertes Epithel) Das Plattenepithel der Tonsillenkrypte hat für das lymphatische Pa renchym die Funktion, den Lymphocyten eine genügende Kontaktzeit mit Antigenen und die Möglichkeit zur Rückwanderung zu bieten

Sowohl im Krypten wie im Oberflächen- epithel der Gaumenmandel konnten wir erst mals *Langerhans Zellen* nachweisen Der elek tronenmikroskopische Nachweis von Langer hans-Zell-Granula ist hierfur beweisend Die vielfältige Struktur der Granulaanschnitte er klart sich durch den dreidimensionalen Aufbau des Langerhans-Zell-Granulum (Wolff, 1967 *b* Sagebiel & Reed, 1968 Itho, 1970).

Die Zellen sollen mesenchymaler Herkunft sein, zumal der Nachweis von Langerhans-Zell-Granula in Histiocyten bei der Histiocytosis X erbracht wurde (Basset et al 1965 De Man 1968 Hashimoto & Tarnowski, 1968 Caputo & Gianotti 1970) Außerdem enthalten die Zellen Enzyme, die typischerweise in Bindegewebszellen gefunden werden (Wolff 1967 *a*) und können phagocytieren (Breathnach & Wyllie, 1965 Mishima, 1966). Eine Abstammung vom Nervensystem ist unwahrscheinlich da in der Epidermis elektronenmikroskopisch niemals ein direkter Kontakt zwischen Nerven und Langerhans-Zellen beobachtet wurde (Breathnach, 1965 Zelickson 1966) und es zu keinerlei Veranderungen an den Zellen in pathologisch denervierter Haut kommt (Breathnach et al., 1962) Gegen eine melanocytäre Herkunft spricht das Fehlen von Prämelanosomen und Melanosomen im Cytoplasma der Langerhans-Zelle und daß im Tonsillenepithel des Menschen keine Melanocyten

vorkommen. Auch die Tatsache, daß in pigmentierten und unpigmentierten Hautabschnitten die Zahl der Langerhans-Zellen pro Flächeneinheit konstant bleibt, die der Melanocyten aber erheblich schwankt, untermauert dies (Wolff 1967 *a*)

Langerhans-Zellen konnten außer in der Epidermis u. a. auch in der Gingiva (Schroeder & Theilade, 1966) und im Cervix Epithel (Hackemann et al., 1968) nachgewiesen werden, so daß ihr Vorkommen in der Tonsille als ein für dieses Organ unspezifischer Befund angesehen werden muß. Da die mit Histiocytosis X bezeichneten Krankheitsbilder (Morbus Hand-Schüller-Christian, Morbus Letterer Siwe und Eosinophiles Granulom) auch die Tonsillen befallen können (Brunner 1951), sollte man sich davor hüten, beim Nachweis von Langerhans-Zell-Granula im Tonsillenepithel falsche diagnostische Schlüsse zu ziehen, weil diese Granula schon unter „Normalbedingungen" in der Tonsille vorkommen.

RESUMÉ

On peut faire varier la formation du réticulum de l'épithélium des cryptes en administrant de la cortisone ou de la désoxycorticosterone. La dimension des coupes épithéliales réticulés évolue, après la naissance, parallèlement à la formation des follicules secondaires. La formation du réticulum est considérée comme un processus physiologique. Au microscope électronique le processus de formation du réticulum se présente de la manière suivante les lymphocytes pénètrent d'abord entre deux cellules épithéliales à travers la membrane basale dans les couches profondes épithéliales. D'autres cellules pénètrent dans l'épithélium par l'orifice ainsi formé. Chez l'homme au schéma de la formation du réticulum se superposent des transformations inflammatoires. Les données morphologiques sont en relation avec la fonction tonsillaire.

SUMMARY

In animal experiments reticulation of the crypt epithelium can be varied by administration of cortisone and desoxycorticosterone. The amount of reticulated thelium in the postnatal period is found to be paralleled by the development of secondary follicles. Reticulation is regarded as a physiologic occurrence. By electron microscopy the pattern of reticulation appears to be as follows: lymphocytes migrate between two epithelial cells through the basement membrane into deeper epithelial layers. Other cells advance through these gaps into the epithelium, where they are found lying between delicate processes of epithelial cells surrounded by edema fluid. In the central and superficial epithelial layers, in addition, lymphoblasts are found in mitosis. Occasionally lymphocytes are seen above an intact basement membrane. In man, inflammatory changes are superimposed on the pattern of reticulation. The morphological findings are brought into relation with tonsillar function. The occurrence of Langerhans-cells in the epithelium of human palatine tonsils is taken into consideration.

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DISCUSSION

I Friedmann Our observations have been identical and confirm the profuse migration of lymphocytes into and through the surface epithelium. This is a most interesting phenomenon and raises several questions. Are these lymphocytes a waste product of lymphoid hyperplasia and are they shed passively or

the tonsillar crypts or onto its surface. There are often small capillaries opening into the surface epithelium which may carry normal or damaged cells. I am, however, not entirely happy with the term "Retikulierung" which might lead to some confusion, at any rate, in the minds of some pathologists. The histopathology of the tonsil presents difficulties and the terminology should be changed and would add to the great value of these investigations.

C. R. Pfaltz: Welche Rolle spielen die Lymphocyten, welche sich während der Retikulierungsphase innerhalb der kryptennahen Epithelschicht befinden? Wo finden nach der Meinung von Herrn Falk die Antigenaufsammlungsprocesse in der Tonsille statt?

P. Falk (Antwort) an Herrn *Friedmann*. Wir verbinden mit der Retikulierung einen anderen Begriff. Unter normaler physiologischer Retikulierung des Tonsillenepithels verstehen wir die folgenden verschiedenen Zustandsbilder am Epithel: Die Retikulierung beginnt mit einer wellenförmig verlaufenden Basalmembran, Lymphocyten liegen unter der eingebuchteten Basalmembran. Zwischen Epithelzellen entstehen Lücken in der Basalmembran, durch welche die Lymphocyten eindringen. Die Epithelzellen gehen durch weitere Lymphocyten auseinander, so daß Lymphocyten und Plasmazellen in einem Ödemsee zwischen den auseinandergezogenen Fortsätzen der Epithelzellen bis zum Stratum superficiale liegen. Dieses Bild ohne Eindringen oder Dazwischenliegen von Kapillaren oder Bindegewebsfasern nennen wir „physiologische Retikulierung". Wachsen infolge einer granulierenden Entzündung bei chronischer Tonsillitis durch die Lücken der Basalmembran zwischen den Epithelzellen Bindegewebsfasern und Kapillaren ein, dann können wir von einer „pathologischen Retikulierung" sprechen, die wir aber bei unseren Untersuchungen nicht feststellen konnten.

An Herrn *Pfaltz:* Da man im retikulierten Epithel neben Lymphocyten auch Lymphoblasten, Lymphoblasten in Teilung und Plasmazellen findet, muß man annehmen, daß schon im Epithel immunologische Vorgänge stattfinden. Die Lymphocyten können als Träger zellständiger Antikörper in das Tonsilleninnere zurückkehren, wo dann die weiteren immunologischen Vorgänge sich abspielen können. Das retikulierte Epithel als eine Kontaktstelle ist unseres Erachtens ein funktionell wichtiges Glied in einem miteinander verbundenen Immunsystem.

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POLYCHONDRITE CHRONIQUE ATROPHIANTE

Ultrastructure des Lésions Cartilagineuses au Niveau du Pavillon de l'Oreille

R. Grimaud et B. Bodelet

Travail de la Clinique O.R.L. de l'Hôpital de Nancy de la Clinique O.R.L. de l'Hôpital de Saint-Dié et du Laboratoire de Microscopie Electronique de Nancy Nancy France

Abstract Après une étude ultrastructurale du cartilage auriculaire humain, les auteurs envisagent les différentes altérations rencontrées chez un malade atteint de polychondrite chronique atrophiante. Si certaines plages conservent la structure classique du cartilage auriculaire, on note une importante dédifférenciation des chondrocytes au niveau des zones atteintes. Cette dédifférenciation se traduit par une perte de la charge glycogénique et par l'aptitude de plus en plus grande du chondrocyte devenu fibroblaste à élaborer des fibres collagènes. La polychondrite chronique atrophiante peut donc être envisagée comme une maladie due à une dédifférenciation progressive des chondrocytes en fibroblastes.

Décrite la première fois par Jahsch-Wartenorst en 1923 la polychondrite chronique atrophiante reste une maladie rare, mal connue, et d évolution fatale. Elle rentre dans le vaste cadre des maladies dites « de système » puisqu elle atteint aussi bien les cartilages auriculaires, que les cartilages articulaires, bronchiques ou septaux.

Les différents tableaux cliniques de cette maladie sont maintenant bien connus, mais il faut reconnaître qu ils ne permettent à aucun moment, d affirmer la polychondrite chronique atrophiante. Seule la biopsie cartilagineuse permet de poser avec le maximum de certitude, ce diagnostic.

Il ne semble pas, de l avis des auteurs, qu il existe une chronologie quelconque dans l'atteinte des cartilages, et l on pourrait tout aussi bien biopsier les anneaux trachéaux (atteints dans 70% des cas selon Dolan) que le cartilage de la cloison (déformé dans 82% des cas) ou encore que le pavillon de l oreille (tuméfié dans 88% des cas). En réalité, ce sera le plus souvent au niveau du cartilage du pavillon que l on fera ce prélèvement. En effet, à ce niveau, il existe généralement des déformations cliniquement faciles à dépister et la biopsie sera moins dangereuse qu au niveau de l arbre trachéo-bronchique ou des cartilages épiphysaires.

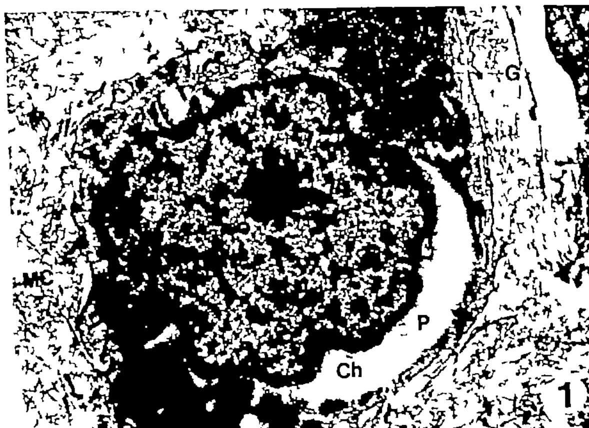
Les lésions histologiques ont été bien décrites en microscopie optique, elles n ont toutefois pas permis d apporter de nouveaux arguments de discussion quant à la pathogénie de l affection. C'est la raison pour laquelle nous avons entrepris une étude en microscopie électronique.

La structure du cartilage auriculaire d'un sujet atteint de polychondrite chronique atrophiante est très nettement dystrophique. Les altérations sont visibles au niveau de la substance fondamentale et au niveau des chondrocytes.

La substance fondamentale

La substance fondamentale du cartilage auriculaire de l'homme comprend deux zones (Fig. 1)

une zone péricellulaire composée de fines



ig. 1 Cartilage auriculaire humain-polychondrite chronique atrophiante. Le chondrocyte (*Ch*) garde sa charge glycogénique (*G*) alors qu'apparaît très nettement le réseau de protofibrilles collagènes (*P*). Noter la densification de la matrice (*MC*). × 2 640.

illes correspondant peut être à la « cap- » des classiques et qui forme la « matrice . »

un réseau de fibres plus épaisses, noyées dans ne substance amorphe et qui constitue pour s anglo-saxons, la substance « inter-territoriale » encore appelée « matrice sombre ».

Le cartilage auriculaire d'un sujet atteint de olychondrite chronique atrophiante se présente au contraire comme un vaste réseau ordonné de fibres collagènes, où il est impossible de reconnaître la matrice sombre et matrice claire. Ce collagène, très dense (. 2, 3) est parsemé de « flaques » de substance « nuageuse » identique à celle que l'on rouvait au sein de la substance inter-territoriale normale.

Les chondrocytes

Il est difficile de parler encore de chondrocytes, tant les cellules observées semblent en avoir perdu peu à peu les attributs.

Leur forme, grossièrement ovalaire, rappellerait volontiers celle des chondrocytes, mais leur pourtour est beaucoup moins dentelé. Les prolongements cytoplasmiques sont en effet moins nombreux, et ils vont diminuer parallèlement au degré de différenciation des chondrocytes. Le noyau des cellules contient encore, comme pour un chondrocyte normal, un nucléole bien visible.

C'est au niveau du cytoplasme que siègent, en fait, les modifications les plus frappantes.

Tout d'abord, on note une diminution de la charge glycogénique des cellules qui va s ame

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Décrite la première fois par Jahsch-Wartenhorst en 1923 la polychondrite chronique atro- reste une maladie rare, mal connue, et d'évolution fatale. Elle rentre dans le vaste cadre des maladies dites « de système » puisqu'elle atteint aussi bien les cartilages auriculaires, que les cartilages articulaires, bronchiques ou septaux.

Les différents tableaux cliniques de cette maladie sont maintenant bien connus, mais il faut reconnaître qu'ils ne permettent à aucun moment, d'affirmer la polychondrite chronique atrophiante. Seule la biopsie cartilagineuse permet de poser avec le maximum de certitude, ce diagnostic.

Il ne semble pas, de l'avis des auteurs, qu'il existe une chronologie quelconque dans l'atteinte des cartilages, et l'on pourrait tout aussi bien biopsier les anneaux trachéaux (atteints dans 70% des cas selon Dolan), que le cartilage de la cloison (déformé dans 82% des cas) ou encore que le pavillon de l'oreille (tuméfié dans 88% des cas). En réalité, ce sera le plus souvent au niveau du cartilage du pavillon que l'on fera ce prélèvement. En effet, à ce niveau, il existe généralement des déformations cliniquement faciles à dépister et la biopsie sera moins dangereuse qu'au niveau de l arbre trachéo-bronchique ou des cartilages épiphysaires.

Les lésions histologiques ont été bien décrites en microscopie optique, elles n ont toutefois pas permis d apporter de nouveaux arguments de discussion quant à la pathogénie de l'affection. C'est la raison pour laquelle nous avons *entrepris une étude en microscopie* électronique.

La structure du cartilage auriculaire d'un sujet atteint de polychondrite chronique atrophiante est très nettement dystrophique. Les altérations sont visibles au niveau de la substance fondamentale et au niveau des chondrocytes.

La substance fondamentale

La substance fondamentale du cartilage auriculaire de l'homme comprend deux zones (Fig. 1)

une zone péricellulaire composée de fines

4

5

Pc
Fi
MP
6
N
Pr
G
G
7

Kollagenfasern zu entwickeln. Die chronisch-atrophische Polychondritis kann sozusagen als eine Krankheit bezeichnet werden.

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DISCUSSION

M. Arslan. L'orateur montre deux cas de polychondrite atrophique chez lesquels l'étude ultramicroscopique de la cartilage confirme les résultats du Mr Grimaud. Selon la pensée de l'auteur ce que les pathologues allemands appellent maladie de Askanazy » est une collagénose dans le domaine ORL.

R. Grimaud. (Réponse) à Mr Arslan: Il est tout à fait justifié de faire rentrer la P.C.A. dans le cadre des maladies mésenchymateuses car il existe des atteintes tégumentaires associées dues à des altérations du derme, altérations portant sur la structure fibrillaire.

Acta Otolaryng 75 112–118, 1973

VAGAL AFFERENT INFLUENCES ON THE PHASIC ACTIVITY OF THE POSTERIOR CRICOARYTENOID MUSCLE

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Abstract The respiratory activity of the posterior cricoarytenoid muscle is strongly influenced by both pulmonary stretch and pressor receptors. These influences are mediated by afferent fibers in the vagus nerves. This demonstration is made possible by the unique anatomic arrangement of the right vagus nerve in the cat, which allows accurate separation of afferent from efferent fibers in its cervical portion.

The primary role of the larynx from a phylogenetic point of view is sphincteric, protecting the lower airway from the intrusion of foreign bodies. In higher species the larynx plays a more definitive role in respiration by assuming a dilator function as well. This is evidenced by rhythmic motor nerve discharges in the laryngeal nerve (RLN) synchronous the inspiratory phase of respiration (Joels Samueloff 1956 Bianconi & Raschi, 1964) Green & Neil (1955) from their observations of impulse activity in the RLN and electromyographic activity in the intrinsic laryngeal muscles, concluded that the abductor muscles contracted during inspiration, the adductor muscles during expiration. Similar findings were demonstrated in human beings by Faaborg Andersen (1957).

Pressman & Kellman (1955) investigated the respiratory movements of the vocal cords in man using high speed cinematography and showed that the glottis indeed widened during inspiration and narrowed during expiration.

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According to Negus (1949) the widening of the glottis preceded a contraction of the diaphragm whereas glottic narrowing heralded the onset of expiration Murakami & Kirchner (1972) however demonstrated that adduction during expiration was not caused by activation of the adductor muscles but by a gradual fall in tonic activity of the posterior cricoarytenoid muscle (PCA)

In further support of the respiratory function of the larynx, it has been demonstrated that under certain circumstances vocal cord movements continue after tracheotomy and that vocal cord abduction precedes any activity in other respiratory muscles (Nakamura et al., 1958).

In this regard, it is generally agreed that the origin of spontaneous rhythmic respiratory activity is located within the medulla, and that this activity is complexly modified by extramedullary nervous influences. These include among others, the effects of discharges from the pons and reflex impulses ascending in the vagus.

Several observations support this idea. Hering (1868) and Breuer (1868) observed that lung inflation inhibited the inspiratory phase of respiration. Head (1889) on the other hand showed that lung deflation resulted in strong inspiratory excitation and that this phenomenon was abolished by freezing the vagus nerves. Widdicombe (1954) reported similar findings

with cooling of the vagus nerves. Moreover electrical stimulation of the superior laryngeal nerve (SLN) in some circumstances inhibits inspiration (Mårtensson 1963)

With specific regard to the respiratory function of the larynx, evidence suggests that the activity of the PCA is influenced by variations in oxygen and carbon dioxide tension, by anesthetic levels and by any stimulation of the larynx or neighboring pharynx (Suzuki & Kirchner 1969).

Variations in intrapulmonary pressures are also important, as evidenced by the decline in phasic activity of the PCA as ventilatory resistance decreases (Sasaki et al. 1972).

These observations therefore suggest that the respiratory function of the larynx originates in the medullary respiratory center and that this respiratory center may be influenced by afferent stimuli of extramedullary origin, chiefly those mediated by the vagus nerves.

It is therefore our purpose to clarify the effects of vagal afferents on laryngeal respiratory function with special regard to the effect of pulmonary stretch and pressor afferents on phasic abductor activity

METHODS

Thirty-one healthy adult cats were used in this experiment. Anesthesia consisted of sodium pentobarbital, 30 mg/kg body weight administered intraperitoneally A uniform degree of anesthesia was maintained throughout the experiment by intravenous augmentation at intervals as necessary

The larynx and trachea were exposed through a vertical midline incision. The strap muscles were then identified and completely removed. The upper half of the sternum was partially resected to obtain further exposure of the superior mediastinum, care being taken avoid injury to the pleura.

The trachea was then transected at the lower margin of the larynx the distal segment cannulated and fitted with a three-way stopcock to facilitate deliberate inflation and deflation of the lung.

The following nerves were then exposed, carefully avoiding injury:

1) right and left SLNs
2) right and left VAGI
3) RLNs (descending)
4) RLNs (ascending)

Our plan was to isolate both descending RLNs at their take-off from the vagus, so as to preserve the motor nerve supply to the larynx while observing the effects of blocking or dividing the vagus just below this point. However the left RLN could not be exposed at its point of origin from the vagus without producing pneumothorax. On the right side, the point of origin was easily identified, the subclavian vein providing a convenient landmark. The RLN usually lies deep to this vein within the carotid sheath at the level of the 15th to 17th tracheal rings (Fig. 1)

Complete vagal de-afferentation was accomplished by blocking or dividing the right vagus below the RLN take-off and the left vagus in the neck. Since the motor supply to the larynx was spared only on the right side the right PCA muscle was used for recording.

In order to eliminate other minor afferents, both SLNs were cut prior to the experiment. Since there is some evidence that the sympathetic system conducts afferent impulses (Cromer et al., 1933), the sympathetic trunks were also sectioned in the neck.

Concentric needle electrodes were used, the EMG being displayed on a multichannel oscilloscope (Tektronix 564 B) with simultaneous amplification on the Grass AM5 sound system.

Intratracheal pressure was measured by a Statham P23BC transducer and displayed in phase on the Tektronix multichannel oscilloscope

In some instances, the peripheral segment of one vagus nerve was divided into single fibers or filaments which were positioned on platinum wire electrodes within a warm mineral oil bath. Neural activity was then displayed

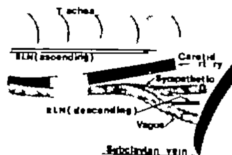


Fig 1 The anatomy of the right vagus in the cat's neck allows selective separation of afferent fibers from efferent (Recurrent Laryngeal Nerve).

oscilloscopically after amplification by a DAM 5 differential preamplifier All oscilloscopic activities were photographed by the Grass camera.

Inflation of the lung was carried out by forcing 30 ml of air directly into the three way stopcock. Deflation was carried out by aspirat ing through the same stopcock before the onset of spontaneous inspiration.

RESULTS

Inflation of the lung

With both vagi intact, the activity of the PCA muscle during inspiration was normally re duced or abolished by inflation of the lungs. On the other hand, when both vagi were divided as described above, lung inflation caused no discernible effect on the existing level of spontaneous activity in the right PCA. It is important to point out that bilateral vagotomy generally resulted in an increased level of inspiratory activity presumably because of interruption of vagal inhibitory fibers. It is upon this level of spontaneous PCA activity that lung inflation had no discernible effect.

Deflation of the lung

With intact vagi, deflation of the lungs normally resulted in accentuation of PCA activity

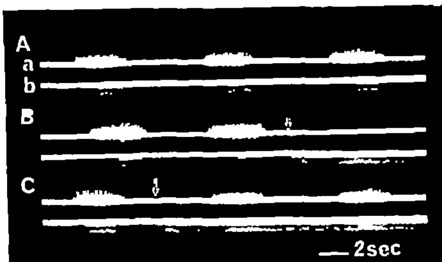


Fig. 2. Vagal afferent influences on inspiratory activity of the posterior cricoarytenoid muscle. (*a*) (Top line in all three tracings). Electromyogram of the right posterior cricoarytenoid muscle. (*b*) (Lower line in all three tracings). Neural potentials in afferent filament in right vagus. *A.* Recording during normal respiration. *B.* At the arrow the lung was mechanically inflated. Posterior cricoarytenoid activity stopped at once, and afferent vagal potentials started, continuing as long as the lung remained inflated. *C.* Same procedure as *B* but after additional section of the left vagus in the neck. Inflation of the lung induced afferent neural potentials, but the right posterior cricoarytenoid muscle continued its phasic activity.

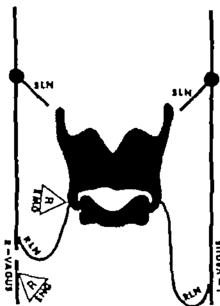


Fig. 3. This figure shows that the pathway of the vagal afferent impulses which inhibit the posterior cricoarytenoid activity in Fig. 2 is the left vagus and that the vagal afferents were recorded from the peripheral segment of the right vagus. *R.* Recording electrode. *EMG.* Electromyogram. *ENG.* Electroneurogram. Both superior laryngeal nerves and both sympathetic trunks have been cut in this experiment and in Fig. 5.

during inspiration. Deflation caused an increase in both duration and frequency of PCA discharges.

After both vagi were sectioned as described above, the level of spontaneous activity appeared unaffected by forced lung deflation.

Increased ventilatory resistance

With the vagi intact, increasing airway obstruction caused strong activity of the PCA muscle and simultaneously induced high negative intratracheal pressures.

After bilateral vagotomy as described above, the level of spontaneous activity in the intact PCA again appeared unaffected by airway obstruction.

PCA activity and afferents through the vagus

Figs. 2 and 4 show simultaneous electromyograms of the right PCA muscle and the afferent electroneurograms of a single fiber preparation of the vagus (Fig. 2, right vagus, Fig. 4 left vagus).

When the lung was mechanically inflated at the end of a normal inspiratory effort, dis-

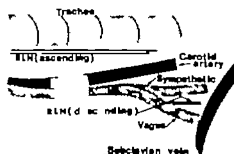


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With intact vagi deflation of the lungs normally resulted in accentuation of PCA activity

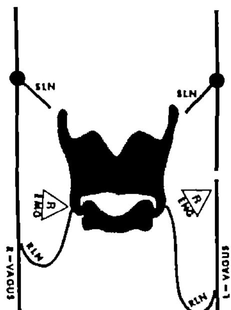


Fig 5 This figure shows that the pathway of the vagal afferent impulses which inhibit posterior cricoarytenoid activity in Fig. 4 is the right vagus and that the vagal afferents were recorded from the peripheral segment of the left vagus.

abolishes the inspiratory activity of the PCA muscle.

2) Forced deflation of the lung results in increased inspiratory activity of the PCA muscle.
3) After vagal de-afferentation, neither inflation nor deflation affects the level of spontaneous respiratory activity in the PCA muscle.
4) Increased ventilatory resistance which presumably stimulates pulmonary pressor receptors induces strong PCA muscle activity
5) After bilateral vagal de-afferentation, increased ventilatory resistance fails to influence spontaneous PCA muscle activity

This study demonstrates that the respiratory activity of the PCA muscle is strongly influenced by both pulmonary stretch and pressor receptors and that these influences are in fact mediated by afferent fibers in the vagus nerves. This demonstration is made possible by the unique anatomic arrangement of the feline vagus which allows accurate separation of afferent from efferent fibers in its cervical portion.

RESUME

L'activité respiratoire du muscle crico-arytenoidien postérieur est fortement influencée par les récepteurs pulmonaires d'étirement et de pression. Les influx provenant de ces recepteurs sont conduits par les fibres afférentes du nerf vague. La démonstration de cette action est facilitée par la disposition anatomique spéciale du nerf vague droit chez le chat; celle-ci permet, en effet, dans la portion cervicale, de séparer précisément les fibres afférentes des fibres efférentes.

ZUSAMMENFASSUNG

Die Atmungsfunktion der hinteren Cricoarytenoid-Muskeln wird sowohl durch die Lungenausdehnung als auch durch die Pressor-Rezeptoren stark beeinflusst. Diese Einwirkungen werden durch zuführende Fasern des Vagus-Nerven vermittelt. Dies kann wegen der ungewöhnlichen anatomischen Struktur als rechten Vagus-Nerven der Katze demonstriert werden, an dem es möglich ist, zuführende und abführende Fasern in seinem Halsabschnitt genau zu trennen.

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DISCUSSION

I Padovan. I have two questions from a more technical point of view

1 Why did Mr Kirchner use in his experiments the cat and not the dog? It is well known that the anatomy of respiration is not the same and the one in a dog is more like that of man, especially the ynx. Since I am sure the difference in price between a cat and a dog in the USA cannot cause a problem there must be another reason for his choice.

2. It would be of interest to know if Mr Kirchner had in mind the investigations by Felberbaum in Leningrad and also those by the group from Mount Sinai Hospital in New York dealing with receptives of the respiratory pathways and especially of the larynx.

E. Loebell. Did Mr Kirchner find different kind of spindles? And were the studies done in relation to the inspiratory airflow? In my electromyographic studies of the diaphragm I found two types of inspiration in humans: most start inspiration with electrical activity of the diaphragm In other cases this activity starts later and lasts longer than the respiratory curve of inspiration.

J A Kirchner (Reply) to Mr *Padovan.* The cat is the best animal for experimental neurophysiology for many reasons, including the fact that their nerve trunks contain very little fibrous tissue, so that nerve fibers can be easily identified, anatomically and physiologically And they are also less expensive than dogs!

Mechanoreceptors in the larynx have been studied by many investigators. Those located in the mucosa have been well described by König of Heidelberg and von Leden of Los Angeles. Those located in the fibrous capsules of the laryngeal joints have been identified morphologically by two Russians, Jankovskaya and Gracheva, and studied physiologically by Wyke and his group in London.

The evidence for muscle spindles is less certain, and varies among animal species. Spiral endings have been photographed by Wyke and Abo-el-Enein, but whether these structures act as genuine spindles is not certain. Mårtensson, for example, has not found physiological evidence for spindles in the laryngeal muscles of the animals he studied.

Nevertheless, the corpuscular nerve endings in the laryngeal tissues undoubtedly serve a protective-reflex function, and may even be important in a feed-back control of the laryngeal muscles during phonation.

To Mr *Loebell.* The posterior cricoarytenoid muscle begins its contraction before the diaphragm, and appears to be influenced by the same changes in pO_2, pCO_2, intrapulmonary pressures, etc.

Regarding your second question, we have observed two types of muscle fibers—or better—motor units in the posterior cricoarytenoid muscle: one type shows the phasic, inspiratory activity and serves to open the glottic. The other type does not show this phasic activity and may have a phonatory function in stabilizing the arytenoid cartilage against the forward pull of the thyro-arytenoid muscle. But I cannot be sure

Acta Otolaryng 75 119–126, 1973

NASOPHARYNGEAL FIBROMA

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Abstract The purpose of this paper is to present my experience on juvenile nasopharyngeal fibroma, a disease which is tremendously frequent in Mexico. We have done some research on its etiology from the points of view of genetics, heredity virus infection, and on treatment.

Since 1956 when I reported 70 cases of Juvenile Nasopharyngeal Fibroma (Tapia Acuña, 1956), many more cases have been seen at the General Hospital and in private practice in Mexico City making a total of 279 within the last 22 years. We saw 15 cases in the first half of 1970 alone, resembling an epidemic disease. The patients came from different altitudes and latitudes, including big towns. This fact caused me believe that a virus and not a hormonal factor might be responsible for it, which has been previously investigated by us and some others.

In all cases here reported, diagnosis was made clinically and confirmed by histopathological examination, which demonstrated the presence of stellar cells supported by immature fibroblasts with tortuous vessels in a stroma of *myxomatous tissue, devoid of elastic* or muscular fibers (Figs. 1–3).

Clinical diagnosis was based on the following symptoms and signs: nasal obstruction, repeated hemorrhages from the nose and pharynx and presence of a hard tumor situated at the nasopharynx, usually involving one or both nasal fossae and one or more facial sinuses and sometimes the orbit or the pterygomaxillary space. The sella turcica or even the brain were involved in a few cases. Ear troubles and infection were sometimes present, pain was rare and the general condition was fair except when the patient had suffered abundant or very frequent hemorrhages. Facial deformities and unilateral exophthalmus with vision troubles (Figs. 4 5) were not rare in our cases. During clinical examination, the tumor was seen to be smooth, grey or reddish, with a tendency to bleed at any contact, manual or instrumental (Fig. 6)

Radiological findings were: presence of a shadow occupying the nasopharyngeal space and one or more sinuses, deformity of the sella turcica, etc., all depending on the elongations and size of the tumor Tomography confirmed the above-mentioned data. Angiography showed vessels surrounding or penetrating into the tumor in a definite way

An examination of the etiology of this disease was started with the purpose of discovering the possible influence of a genetic defect or a virus infection in the development of the tumor Thirty-five patients were studied by the geneticist and some fresh specimens were sent *to the virologist to look for unknown virus.*

I may sum up the results of this study and our own clinical experience as follows:

(*a*) The ages of the patients ranged from 10 to 25 years. Recently I saw a patient 35 years old having a large nasopharyngeal fibroma. He had been operated at the age of 17 years for the same complaint, without improvement, which explained the persistence of the disease.

(*b*) We have never seen a case of juvenile nasopharyngeal *fibroma in females. In all cases*



Fig 1 Hyaline fibrous tissue. Oppressed vessels. Limit of the tumor at left ×36.

studied, the patients were male, having normal genital organs and the XY chromosome pair

(*c*) There is no relation between heredity and the development of the tumor All examined patients had a normal karyotype and no abnormality or genetic disease was found either in them or in their relatives.

(*d*) Most of the patients were Mexican natives. The remainder were mustee or of European extraction

(*e*) No specific infection has been found. Only common flora of the respiratory tract and a few adenovirus were present in the specimens sent for virus study

(*f*) Slight increase in white blood cells and decrease in red cells and hemoglobin was the only pathologic finding in blood tests, though not in all cases.

(*g*) Biopsy is unnecessary if a correct clinical diagnosis has been established. Sometimes biopsy could be dangerous because of the possibility of causing a severe hemorrhage that



Fig 2 Fibroblasts, myxomatous tissue and vessels. No elastic fibers ×36

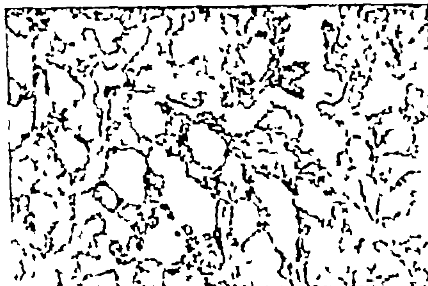


Fig 3 Multiple vascular canals. 36

might impair the patient's general condition or the surgical treatment more difficult.

Medical treatment is useful only to prepare patient for surgery but will not cure him. Radium, X ray and cobalt therapy have failed our hands. Electrocoagulation might be of p in cases of small or residual tumors, ough results are not always satisfactory rogens or any other hormonal administra not only do not help, but produce unle side effects. In addition, I have tried otocoagulation to assess its destructive ac on on specimens of this kind, though without itive results.

Surgery remains the method of choice. Usully we do it when the general condition of he patient is at its best. Nevertheless, re al of the tumor has sometimes been considered urgent due to massive or too frequent emorrhages or when its size is compromising ision or other function We have observed small, better than large blood transfusions few days before operation are helpful. Dur operation, we transfuse 1 000 cc of blood. bation for anesthesia through a tracheal toma instead of through the mouth, is pre erred when the tumor is too large.

The surgeon has to bear in mind three oblems, which are: a proper approach, a complete removal of the tumor and control of hemorrhage during operation. The usual way is the retropalatine approach. I perform a horizontalincision on the soft palate. The tumor is then seen through this window The surgeon s finger is introduced through the incision to palpate the tumor assess its size ex tension, point of origin, adherences and everything which is useful for a good dissection. After pulling out and upward the soft palate, the tumor is held with a proper forceps, the finger is replaced into the opening and will serve to guide a dissector or curette, which is introduced via one nostril in order to make



Fig 4 Facial deformity Fibroma was removed by the combined oral and retropalatine approaches.



Fig 5 Exophthalmus. The deviated eye returned to its place after removal of the tumor

the dissection An assistant pulls the forceps downward and once the tumor has been isolated, it comes out without difficulty The procedure has to be done rapidly to avoid excessive blood loss. Hemostasis by packing is the following step.

In some cases it was necessary to perform later rhinotomy with or without partial removal of the skeleton, combining this approach with the one mentioned above. I had to open through the mouth the pterygomaxillary space four times and once to open it through the maxillary sinus. On two occasions I did not dare to remove the whole tumor because it had extended too far into the cranial fossa. The most amazing case I have yet seen is that of a boy 12 years old who had part of the tumor inside the brain (Figs. 7 8), without disturbing his vision or causing troubles other than those commonly seen. I was able to reach the opening of the cranial fossa and I cut the tumor at this level. An expert neurosurgeon performed temporal lobectomy but he could not remove the remaining tumor because he found difficulty in dissecting it and controlling the hemorrhage This patient left the hospital apparently in good condition. He came to the otolaryngological department one year later with a slight difficulty in walking His nose and nasopharynx were free from tumor reflexes were normal as well as his psychological sphere. He refused a new examination, which would have been of interest.

In our series we have to regret just one fatality which occurred 17 hours after removal of the fibroma by lateral rhinotomy The



Fig 6 Specimen: the middle fragment was located at the sphenoidal sinus; fragment at left was at the pterygomaxillary fossa.





Figs. 7 and 8. Intracranial nasopharyngeal fibroma.

surgeon could not convince the parents of the patient to authorize autopsy. Recidives or residual tumors have been observed in 25 cases (9%). Most of the patients were operated on. Others were treated by electrocoagulation.

In conclusion I believe that the frequency of cases is related to race and nutrition. Surgery is the method of choice for treatment. Cryosurgery as used by Miller (1969) and others might be a good solution to the problem of hemorrhage. I am satisfied with the results of our procedures, though I think that there are still ways of improving them. Work has to be done in the field of immunology for prevention of the disease, which is impossible, so far.

RÉSUMÉ

Le but de ce travail est de faire connaître notre expérience sur le nasofibrome juvénile dont la fréquence est extraordinaire au Mexique. Nous avons fait des recherches du point de vue causal, en tenant compte des facteurs génétiques, héréditaires et viraux. Les résultats du traitement sont analysés.

ZUSAMMENFASSUNG

Der Zweck dieser Arbeit ist, unsere Erfahrungen über das in Mexiko bei Jugendlichen ausserordentlich verbreitete Nasenrachenfibrom darzulegen auf Grund von Untersuchungen über die Ursache, wie genetische, erbliche und virale Faktoren.

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Fig 1 (*a*) Angiography of the internal carotid, left side, frontal projection. Contrast filling the tumour area.

DISCUSSION

G Hall. In Norway this disease is not as common as it apparently is in Mexico. The treatment also in our country has been extirpation, which, as mentioned, often leads to severe haemorrhage. In one of our cases, this became so severe during the first operation that upon recurrence, we operated in hypothermia and employed extracorporal circulation.

The patient was a 20-year-old boy suffering from a blocked but running nose for the past . years. A tumour in the left side of the epipharynx was discovered in the local hospital, and upon admittance in the State Hospital an angiography revealed that its blood supply came from the left carotid. A hypertrophy of the ascendant palatinal and the ascendant and descendant pterygoidal arteries was found, and, in addition, a destruction of the dorsal part of the bony palate. The tumour was removed, followed by a severe haemorrhage: three bottles of blood were infused. Following a new haemorrhage 4 days later we had to ligate the external carotid on the left side.

Twenty days after the operation he was discharged, but a new growth of the tumour was seen after only 6 months. The patient had swallowed a good part of the tumour but still the epipharynx was filled up. A new angiography showed an abnormal blood supply from the carotid siphon to the tumour via the ophthalmic artery (Fig. 1 *a* and *b*).

Hormonal therapy and X-ray therapy were discussed, but rejected. The patient was able to work for about 2 years, but then something had to be done and operation in hypothermia and extracorporal circulation was decided upon.

X-ray tests with compression were performed to see whether the brain had sufficient blood supply from either side alone and also tomometry of the eyes to see whether a compression of the left internal carotid would interfere with the sight of the left eye.

Fortunately these tests showed favourable conditions, and there were no serious contraindications. The operation was performed in March, this year.

The sternum was split, cannulas were introduced through both caval veins, the right femoral artery and



Fig 1 (*b*) Angiography internal carotid, left side. Contrast filling the tumour area via the ophthalmic artery (→).

the apex of the left ventricle into the heart. The cooling went down to about 16°C, measured in the oesophagus. The total perfusion time was 2 hours and 50 minutes. The approach to the tumour was a combined transpalatinal and transpharyngeal one. A part of the hard palate was chiselled out, the tumour removed and a tampon introduced. Six litres of blood were infused, in addition 2 l postoperatively and another litre when the tampons were removed. The condition of the patient was good throughout the intervention, and he was declared to be fit for work after 1 months.

J E Cowley Please describe the technique of using the finger there the palate and instruments used in this operation and clarify the rate of local recurrence, mortality and inoperable status. And also add a word of caution re the use of silicone spheres in the treatment of these tumors due to the possibilities of intracranial complications.

R Albrecht Dr Acuña hat das Glück im absoluten Häufigkeitsgipfel des Nasenrachenfibroms tätig zu sein. Auch in Indonesien und in Teilen des vorderen Orients ist es nicht so selten wie z.B. in Europa. Daher dürfen wir von Ihm die Beantwortung von Fragen erhoffen, die an Hand von Einzelfällen nicht recht zu klären sind. So darf ich fragen, ob in Mexico eine familiäre Disposition für das Nasenrachenfibrom zu finden ist. Auch die Chromosomenanalyse wäre an einer so grossen Zahl Erkrankter sicher aussagekräftig. Bisher wurden bei nur vereinzelten Untersuchungen eine Abweichungen gefunden. Die Frage einer viralen Infektion dieser eigenartigen Geschwulst ist noch nicht definitiv entschieden. Wir haben sie elektronenoptisch überprüft. Dabei fanden wir die eigenartigen, für das Nasenrachenfibrom spezifischen Kernelnschlusskörper von denen wir bisher nur wissen, dass sie nichts mit Viren zu tun haben und dass sie keine Ribonukleinsäure enthalten. Sinn und wirkungsvollster Weg einer möglichen Hormontherapie ist an einem grossen Krankengut natürlich auch am ehesten beurteilbar und ich möchte fragen, welche Erfahrungen hier bereits gemacht wurden. Wir müssen unverändert, wenn auch nur an Hand weniger Fälle bestätigen, dass das Tetranatriumsalz des 4 4-Dihydroxy-α,β-diäthylstilbendiphosphats allen bisherigen Oestrogenpraeparaten überlegen ist und auch in vitro die Zellteilungsrate des Nasenrachenfibroms beeinflusst. Es führt regelmässig zur Rückbildung der Geschwulst und ist deshalb in besonders problematischen Fällen ein wertvolles Hilfsmittel.

U Schröder Just a surgical tip: If the nasopharyngeal fibroma is preoperatively filled with solution saline containing few drops of adrenalin and the injection is made with pressure it will anemize the tumour which is then easier to remove.

R Tapia Acuña (Reply) to Mr *Hall*. I have never seen a case like the one you mentioned. We usually transfuse 800 cm³ to 1 000 cm³ of blood during operation. The worst case I ever saw was that of the boy who had a big part of the tumor inside the brain. This case is already described in the paper. The short time I devoted to present it did not allow me to explain it clearly enough.

to Mr *Cowley*: I believe that ligature of carotid maxillary artery is unnecessary since bleeding during operation is approximately the same. The

me to guide the dissector which is introduced through one of the nasal fossae. I have with me a super-8 film showing my surgical technique. I hope Mr Conley will be able to see it sometime.

Only twice could I not remove the tumor totally. This fact is also mentioned in the paper. In my whole series we had to regret the death of one patient operated by somebody else by lateral rhinotomy. Recurrence or residual tumor was observed in 9% of the cases.

to Dr *Albrecht*: Of course we have tried diethylstilbestrol for treatment of the nasopharyngeal fibroma, but without positive results. On the contrary, it produces undesirable side-effects, as has been shown on one of my slides. It has been demonstrated that there is no genetic or virus factor in the development of the tumor.

to Mr *Slizak*: I do not agree with your suggestion because it is much better not to touch the tumor unless for its removal. It might bleed or create adherences, making surgery more difficult.

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HOMOTRANSPLANTATION OF CANINE TRACHEA AFTER DENERVATION OF THE SPLEEN

A Preliminary Report

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The rejection phenomenon has been the obstacle to advances in organ transplantation, immunodepression has been only partially effec in controlling rejection. The role of the spleen in rejection of transplanted tissues is still but poorly nderstood. We have performed trachea transplanta which are based upon an observation that the jection phenomenon can be altered through de vation of the spleen. The results of these experi will be discussed.

In the treatment of tracheal stenosis it might of advantage if transplanted material could used. We have therefore made experiments ith tracheal homotransplants in dogs. This is preliminary report of these experiments.

In a symposium on Tissue and Organ Transantation, writing about the scope of cartilage rafting, Gibson—a senior lecturer in tissue ansplantation at Glasgow University—says: 'Since allograft cartilage behaves precisely as an autograft there would be little need for the er" This characteristic is due to the unique possessed by cartilage of not provok g an immune response when transplanted ogenically According to Gibson the laryn- and tracheal cartilages would be ideal for reconstruction after an operative excision in is anatomical area, but he wonders: "How an one create from autogenous sources the ucous lining, the muscles, or the intercon- ting fibrous tissue?

The opinion of Gibson concerning the use of tracheal cartilage as allograft may be considered very optimistic. Alonso et al. (1972) performed homotransplantations experimentally on dogs and found that the 8 and 12 month tracheal specimens (two-thirds of the tracheal circumference) showed complete resorption of the transplant. They stated that "by avoiding the mechanical pitfall of replacing the entire tracheal lumen, partial success with allografts is possible"

It seems that if permanent preservation of the cartilaginous arches in a tracheal segment transplanted as allograft were possible, this would raise hopes of a satisfactory outcome in severe cases of stenosis of the trachea.

Although Gibson maintains that a cartilaginous allograft takes and heals well, it is apparent that the phagocytosis occurring in tracheal cartilaginous arches is a rejection response and its elimination might extend the survival time of these arches.

There are tissues in a transplanted tracheal segment—it is a composite graft—which differ in the ability to provoke immune responses. Cartilage causes the least intense reactions whereas mucous membrane muscle and other transplanted tissues produce a stronger response.

We decided to test whether the rejection response can be suppressed or eliminated by applying Toivio's new theory of the effect exerted by splenic denervation on this phenomenon.

Toivio has recently put forward a theory according to which the spleen is the centre through which the host's immune response to a transplant is primarily directed, and that immunological information is transferred to the lymphocytes within the spleen by some hitherto unknown neurological mechanism. On the basis of this theory the authors have subjected eight adult dogs to total splenic denervation, but not splenectomy At the time of denervation and in several dogs later as well, skin homografts from unrelated mongrel dogs have been applied. The authors report that, in every case some or all of the grafts survived without the use of any other form of immunosuppression. At the time of the report the longest survival was 18 months.

This theory sounds surprising and perhaps unbelievable but, if it proves correct, will create quite new possibilities for tissue transplantation

As mentioned, our experiments with transplantation of canine tracheal homografts were made in an attempt to discover whether the ervated and control dogs differed in homo- t acceptance

According to the literature (Ferguson et al., 1950; Greenberg, 1958 Fleming & Hommerich, 1968 Tala & Maamies, 1968 Kornmesser 1970; Alonso et al., 1972) the fate of a homotransplant of dog's trachea is as follows. Two weeks after transplantation there is hyperemia and edema at the anastomosis. Two to four months after it there is granulation tissue lining the transplanted mucous membrane The cartilaginous arches of the transplant undergo phagocytosis. This takes place gradually and is completed in 8 to 12 months. Two to four months are required for squamous epithelium to take the place of granulation tissue as lining membrane of the graft. After 4 to 6 months this is again replaced, by ciliated columnar epithelium with minimal submucosal infla matory reaction During this period the su rounding muscle fibres atrophy and under hyalin degeneration

Lymphocytic collections are seen at the fo of resorption of the transplanted cartila and there occurs universal perivascular lymph cytic cuffing throughout the grafted area

Because of concentric scarring the tra planted segment is shortened and the trache wall becomes thinner and the lumen narro If the transplanted piece of trachea is lo enough this can result in collapse of the trach and suffocation of the animal.

According to Kornmesser (1970) and Fle ing & Hommerich (1968) the autotransplant tions of tracheal segments containing 3 to cartilaginous arches have been successful.

MATERIAL AND METHODS

Our material consists of 16 dogs of which were denervated and 8 were control animal In each of a pair of dogs a window only wa made in the anterior tracheal wall and th excised quadrangular pieces of tracheal wa were interchanged. In all the others a segmen consisting of the whole circumference of th trachea enclosing 4–5 tracheal arches and th corresponding membranous part were ex changed. The operation was performed b Hypnostan anesthesia. The dogs were treate with a combination of penicillin and strepto mycin postoperatively They did not get an form of immunosuppression therapy with th exception of the denervation of the spleen.

The condition of the transplant was exam ined by endoscopy and endoscopic photo graphy X-ray films and excision and histo logical examination of the transplanted se ment. In 2 dogs the exchange of tracheal seg ments was made twice All the dogs survived the operation well.

After being cut off from the supplying blood circulation the transplanted piece of trachea was sutured into place in the new host. It is natural, then that the parts of the transplant

immediately adjoining the tissue of the host, i.e. the external portions, will fairly soon obtain adequate nutrition. The mucous membrane within the transplant, however is disconnected from the supplying circulation for a longer time. This of course causes damage to the mucosa. The cartilaginous arches and the tissues joining them suffer least injury through the transplantation. The shorter the transplanted segment is, the better are the chances of survival. The final fate depends on the reaction of the host.

The specimens for histological study were obtained by excising the transplanted part of the trachea 8 to 130 days after transplantation. The tracheal stumps were sutured together and the dogs usually survived the procedure.

RESULTS

hen considering the possible effect of de nervation on the "take" of the transplanted piece of trachea we know from earlier investigations that the transplant gradually disappears and is replaced by tissue growing into the transplant from adjacent structures of the host. If in denervated dogs, we were to find a weakened rejection or permanent acceptance of transplanted tissue, this would be evidence a changed reaction of the recipient dog.

Several factors seem to have influence upon he fate of the homotransplanted tracheal seg- Such factors are the width of the transplant compared with the recipient dog's tracheal lumen, the length of the transplant, possible infection or hematoma, the technique of peration, the histocompatibility of the two gs and the antibiotic therapy In these cir imstances the evaluation of the significance one single factor such as denervation of the cipient dog's spleen, proved to be very dif icult, particularly when the time of observation has not been long enough.

Comparison of the two groups (denervated nd control dogs) revealed in both of them, ring the first 2–3 weeks after transplantation, disappearance of the mucous membrane and its replacement by granulation tissue. Gradually this was covered by new epithelium. The growth of this epithelium seemed to be more advanced in the denervated dogs. Forthcoming investigations will probably indicate whether this epithelium originates from the transplanted specimen or from the host animal. There was a marked infiltration by lymphocytes and phagocytosis of the cartilaginous arches. In denervated dogs these rejection phenomenona were somewhat less marked. The difference is however just a matter of degree.

The question whether the denervation of the recipient dog's spleen has some influence upon the fate of the tracheal transplant or not—which was the aim of our investigation—cannot yet be fully answered. As mentioned, the immediate rejection response seems to be somewhat weaker in the denervated dogs, and we have two denervated dogs with very good preservation of the cartilaginous arches of the transplanted tracheal segments after 100 and 130 days respectively. None of the control dogs have obtained such a good result. However still more evidence is needed. We are continuing our experiments for the purpose of finding out what is the final fate of homotransplanted tracheal segments in denervated dogs.

It seems that for the elimination of the rejection response of the transplanted tracheal homograft it would be of advantage to combine denervation of the recipient dog's spleen with some other means or agent for immunosuppression.

RESUMÉ

Le phénomène de rejet a constitué le plus grand obstacle au progrès de la transplantation des organes. L'immunodépression a été seulement partiellement effective à controler le rejet. Le rôle de la rate dans le rejet de transplantations est encore très peu connu. On a récemment fait des transplantations de la trachée basées sur une méthode où le phénomène de rejet est changé grâce à une dénervation de la rate. Le résultat de ces recherches sera présenté et discuté.

ZUSAMMENFASSUNG

Die Abstossung des verpflanzten Gewebes ist bisher das grösste Hindernis für den Fortschritt der Organtransplantationen gewesen, und mit Hilfe der Immunodepression konnte die Abstossreaktion nur teilweise beherrscht werden. Welche Rolle die Milz bei der Rejektion des transplantierten Gewebes spielt, ist immer noch mangelhaft bekannt. Wir haben Trachea Transplantationen beim Hund ausgeführt, die auf der Beobachtung beruhen, dass die Gewebabstossung durch Denervierung der Milz verändert werden kann. Die Resultate dieser Experimente werden besprochen.

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DISCUSSION

G Yannoulis: Wollte mir die Frage erlauben: O Sie die Optimum-Zeit zwischen der Entnahme d Trachea und ihrer Transplantation bezüglich ihr Wiederbelebungsfähigkeit festgestellt hätten?

Wir haben nämlich bei unseren Homotransplan tionen des Tympano-ossikulären Systems als optima Zeit, das Ende der zweiten Woche nach der En nahme für die Transplantierung konstatiert m möchten wissen, ob vielleicht das gleiche für die Tr chea-Homotransplantation, vorkommt.

H H Naumann. Die interessanten Befunde vo Herrn Siirala sind sehr aktuell, denn die plastisch rekonstruktiven Massnahmen an der Trachea werde angesichts der wachsenden Jahre der Trachealstenos immer wichtiger Sicher besteht kein Zweifel, da Knorpel ebenso wie Knochen als Homotransplan ein Antigen ist wenn auch ein vergleichsweise schwa cher Gibson hatte also sicher nicht recht, wenn glaubte, dass homologer Knorpel unverändert Wirtsorganismus inkorporiert würde Wegen der rel tiv schwachen Immun-Aktivität ist es nun freilich b derartigen Transplantaten nicht leicht, immunologisch Gewebsreaktionen morphologisch sicher abzugrenz gegenüber banalen entzündlichen Phänomenen. Wi hatten das gleiche Problem, als mein Mitarbeit Dr Kastenbauer die immunologische Potenz von ho mologen Knochentransplantaten im Bereich des Mitt ohre untersuchte. Er half sich dadurch, dass er zu Akzentuierung der immunologischen Gewebsreaktio nen die sogenannte „second-set reaction" zu Hil nahm Damit wurde die Deutlichkeit der Befund erheblich besser Deshalb meine Frage: Haben Si für die Beurteilung der Antigenizität der Tracheal transplantate ebenfalls von der Möglichkeit de „second-set-reaction" Gebrauch gemacht?"

T Palva. I should like to comment on the "theory" of Toivio in tissue acceptance. It does not take into account the known facts, e.g. that the "killer cells" the T-lymphocytes, mature by passing through the thymus, or that the human leucocyte antigen is one of the greatest obstacles in tissue transplantation. Nevertheless, my immunological colleague, Dr Rantio, had Dr Toivio to do some spleen denervations for him on dogs, and in all of these a classical tissue rejection became apparent. What Dr Toivio had interpreted as infections were in reality rejection phenomena caused by the lymphocytes.

P M Kiurakene: I think it was important to stress that th opinion of Gibson may be observed Cartilage may also possess immune responses not so important as of skin and muscle.

A second point is the difficulty to have an early idea of the rejection in the control over experimental conditions.

For these reasons we prefer to have biochemical results, such as the dosage of the LDH fractions. In our experiments the only way to have no response in cartilage transplantation is to go through cultures of cartilage.

U Siirala (Reply) to Mr Yannoulis Two weeks must be the best interval

To Mr *Naumann.* The second-set procedure has been used in our skin transplant studies.

To Mr *Palva:* (Rannio): I do not know very much about the experiments in Oulu, but according to what I have heard, the transplanted pieces of skin were badly infected.

To Mr *Kleyskens:* I am very thankful for the remarks, which we will consider when continuing our transplantation work. The whole problem of organ transplantation is a very difficult one.

The report given is a preliminary one.

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VÉRIFICATION EXPÉRIMENTALE SUR L ANIMAL DE QUELQUES ASPECTS ÉLECTRO-COCHLÉOGRAPHIQUES DE LA PATHOLOGIE HUMAINE

M. Portmann J M. Aran[1] et Ch. Coste

Travail du Laboratoire d'Audiologie Expérimentale du Centre de Phono-Audiologi Régional Clinique Universitaire d'O.R.L., Bordeaux France

Abstract Les premiers résultats d'une série d'expérimentations visant à reproduire chez l'animal les différents types de réponses du nerf auditif observés dans la pathologie humaine sont rapportés. 5 cobayes équipés d une électrode à demeure sur la fenêtre ronde (oreille gauche) ont été soumis à des traumatismes sonores (bruit blanc 110 dB) répétés (6 fois 6 heures). L évolution des réponses du nerf auditif au clic et aux différents clics filtrés est observée en enregistrant régulièrement avant pendant et après la série de traumatismes. Le microphonique cochléaire est également mesuré au début et à la fin de l'expérimentation. Au moins 5 semaines après le dernier traumatisme des enregistrements de contrôle sont effectués sur les oreilles droites et, après sacrifice du cobaye, les organes de Corti des cochlées droite et gauche sont observés en microscopie à contraste de phase (surface preparations). Chez les 5 cobayes on observe, à la fin de l'expérimentation, des réponses du nerf auditif en t point comparables à celles observées chez me dans les cas de réponses *dissociées*, typiques surdités professionnelles. Les cochléogrammes révèlent des organes de Corti soit normaux, soit présentant de légères destructions des cellules ciliées externes, principalement au niveau de 2e et 3 tours.

Lors de l enregistrement des réponses du nerf auditif chez l'homme que nous effectuons depuis plusieurs années en tant qu examen diagnostique périphérique dans la surdité, selon la méthode électro-cochléographique (Aran & Le Bert, 1968 Aran et al. 1971), nous observons très souvent, entre autres, deux types de réponses particuliers qui semblent correspondre à des lésions très caractéristiques de l organe de Corti. Ce sont les réponses des types *recrutant* et *dissocié* qui ont été décrits fréquemment et dont deux exemples sont représentés sur les Figs. 1 et 2 (Portmann et al. 1972 Aran 1971)

La comparaison de leurs caractéristiques respectives tant cliniques et audiométriques qu électro-cochléographiques avec celles des sujets normaux (Fig. 1) suggère immédiatement que l on est en présence d une atteinte des structures sensorielles et/ou nerveuses *externes* généralisée tout le long de la membrane basilaire dans les cas recrutants (Fig 1) et, dans les cas dissociés, localisée uniquement au premier tour de spire ainsi que l'indiquent l'audiogramme et les réponses du nerf auditif au clic non filtré et au clic filtré aigu (Fig 2). Les structures moins sensibles (internes) seraient préservées, au moins partiellement, dans les deux cas.

Ce sont ces deux types de réponses que nous avons voulu tout d'abord reproduire chez l'animal afin d en vérifier le bien fondé des interprétations et d en approfondir les mécanismes.

Nous rapportons donc ici les premiers résultats d'une recherche à long terme dont l aboutissement sera, une fois qu on aura reproduit chez l animal tous les types de réponses observés chez l homme et qu on aura pu y faire correspondre des bilans anatomo-pathologiques précis, d un intérêt diagnostique considérable en même temps que très enrichissant

[1] Chargé de Recherche à l'I.N.S.E.R.M.

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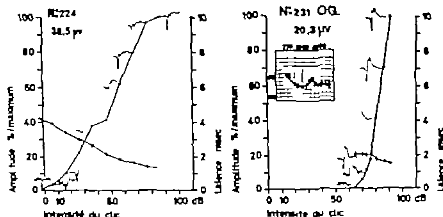


Fig 1 A gauche électro-cochléogramme normal chez un enfant. A droite électro-cochléogramme typique *recrutant* et audiogramme correspondant. (Stimulations par clic non filtré) (sur cette figure et les suivantes une déflexion vers le bas correspond à la cochlée negative par rapport à l'électrode de référence dorée des traces 10msec. — db normal Hearing Level » H. L.)

sur le plan de la connaissance du fonctionnement du récépteur auditif

Désirant reproduire chez le cobaye des réponses *recrutantes* nous avons d abord obtenu des réponses *dissociées* ce qui, compte tenu du fait que celles-ci se situent entre les réponses normales et les réponses recrutantes, reste très logique.

Ce sont les résultats d'une première série expérimentale portant sur 5 cobayes soumis à des traumatismes sonores et dont les réponses sont enregistrées d'une manière tout à fait comparable à l électro-cochléographie humaine (même matériel, même procédure) que nous décrivons ici.

MÉTHODES

Animaux « chroniques »

Les expérimentations consistent à faire subir à des cobayes normaux des traitements oto-destructifs tels que l on obtienne des formes de réponses définies à l avance. Il a semblé que seule l'observation continue des réponses permettait, en contrôlant leur évolution au cours des différents traitements, de doser ces derniers et de les répéter jusqu à l obtention des réponses désirées.

Pour cela nous avons travaillé avec des cobayes équpés d une électrode à demeure sur la fenêtre ronde (oreille gauche) selon une technique mise au point précédemment dans le Laboratoire (Portmann et al., 1966). Les électrodes indifférente et masse étant prises sur les vis servant à maintenir le connecteur cimenté sur le crâne.

Stimulations sonores

Une difficulté dans l'utilisation de l'animal éveillé réside dans la manière de délivrer les clics au tympan. Cela est très difficile à réaliser en champ libre car le moindre mouvement de la tête du cobaye modifie à la fois l'intensité et la forme du signal sonore, ainsi que son temps de propagation depuis le haut parleur jusqu au tympan. Cela est particulièrement incompatible avec la sommation, dans un moyenneur des réponses successives lors de stimulations répétitives.

C'est pourquoi les stimulations sonores sont délivrées directement au tympan par l'intermédiaire d'un tube plastique coudé que l'on introduit dans le conduit auditif externe (Fig. 3) en même temps que l on branche le préamplificateur sur les broches du connecteur fixé sur le crâne et auxquelles sont soudées les électrodes. Le tube est relié à un écouteur

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Abstract Les premiers résultats d'une série d'expérimentations visant à reproduire chez l'animal les différents types de réponses du nerf auditif observés dans la pathologie humaine sont rapportés. 5 cobayes équipés d'une électrode à demeure sur la fenêtre ronde (oreille gauche) ont été soumis à des traumatismes sonores (bruit blanc 110 dB) répétés (6 fois 6 heures). L évolution des réponses du nerf auditif au clic et aux différents clics filtrés est observée en enregistrant régulièrement avant pendant et après la série de traumatismes. Le microphonique cochléaire est également mesuré au début et à la fin de l'expérimentation. Au moins 5 semaines après le dernier traumatisme des enregistrements de contrôle sont effectués sur les oreilles droites et, après sacrifice du cobaye les organes de Corti des cochlées droite et gauche sont observés en microscopie à contraste de phase (surface preparations). Chez les 5 cobayes on observe, à la fin de l'expérimentation, des réponses du nerf auditif en t point comparables à celles observées chez dans les cas de réponses *dissociées* typiques surdités professionnelles. Les cochléogrammes révèlent des organes de Corti soit normaux, soit présentant de légères destructions des cellules ciliées externes, principalement au niveau de . et 3 tours.

Lors de l enregistrement des réponses du nerf auditif chez l homme que nous effectuons depuis plusieurs années en tant qu examen diagnostique périphérique dans la surdité selon la méthode électro-cochléographique (Aran & Le Bert, 1968 Aran et al. 1971), nous observons très souvent, entre autres, deux types de réponses particuliers qui semblent correspondre à des lésions très caractéristiques de l'organe de Corti. Ce sont les réponses types *recrutant* et *dissocié* qui ont été déc fréquemment et dont deux exemples sont présentés sur les Figs. 1 et 2 (Portmann et 1972 Aran 1971)

La comparaison de leurs caractéristiq respectives tant cliniques et audiométriq qu électro-cochléographiques avec celles sujets normaux (Fig. 1) suggère immédia ment que l on est en présence d une atte des structures sensorielles et/ou nerve *externes* généralisée tout le long de la me brane basilaire dans les cas recrutants (Fig et, dans les cas dissociés, localisée uniquem au premier tour de spire, ainsi que l'indiqu l audiogramme et les réponses du nerf aud au clic non filtré et au clic filtré aigu (Fig. Les structures moins sensibles (internes) raient préservées, au moins partiellement, d les deux cas.

Ce sont ces deux types de réponses que no avons voulu tout d'abord reproduire chez l'a mal afin d en vérifier le bien fondé des int prétations et d en approfondir les mécanism

Nous rapportons donc ici les premiers sultats d une recherche à long terme do l aboutissement sera, une fois qu on aura produit chez l animal tous les types de répon observés chez l homme et qu on aura pu faire correspondre des bilans anatomo-path logiques précis, d'un intérêt diagnostique co sidérable en même temps que très enrichiss

[1] Chargé de Recherche à l'I.N.S E R M

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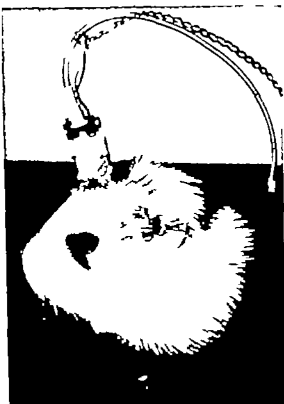


Fig 3 Cobaye équipé de l'électrode sur la fenêtre ronde (oreille gauche). Branchement des électrodes et du tube amenant la stimulation sonore de l'écouteur à l'intérieur du conduit auditif externe.

le *potentiel d action global* (dans lequel le microphonique cochléaire est éliminé grâce à l inversion de la stimulation sonore) de 10 en 10 dB depuis le seuil jusqu à 130 dB Pour le clic et les clics filtrés 8 000, 4 000 et 2 000 Hz la fenêtre est de 10 msec, avec un délai de 1 msec entre l ouverture de la fenêtre et l'arrivée du clic au tympan elle est de 20 msec pour le clic filtré 1 000 Hz. Enfin on enregistre également le *microphonique cochléaire* (alors sans inverser la stimulation) à 110 dB pour le clic et 130 dB pour les clics filtrés avec des fenêtres respectivement de 5 2, 4 8 et 16 msec.

Mesures

Comme pour l électro-cochléographie on mesure sur chaque réponse l'amplitude crête-à crête et la latence. Si les latences des pics N1 N2 etc. sont sans ambiguité dès le seuil sur les réponses normales, ce n est pas le cas, comme on le verra dans les résultats, dès que les réponses sont déformées. En effet il est à ce moment là plus difficile de reconnaître les dif férents pics présents dans la réponse. C'est pourquoi, bien que nous mesurions leurs la tences respectives, nous ne représentons, sur les courbes entrée–sortie, que le délai entre la stimulation sonore et le point le plus négatif de la trace. Celui-ci corespond alors, suivant les amplitudes relatives des différents pics, à N1 ou à N2 voire N3 etc.

Les valeurs de l amplitude et de la latence sont mesurées directement sur l'écran de l oscilloscope et les réponses sont ensuite enregistrées sur papier avec une amplification telle que la dimension du tracé soit toujours sensiblement la même. Cela afin de pouvoir plus facilement comparer les formes des dif férentes réponses entre elles.

PROTOCOLE EXPÉRIMENTAL

Cinq cobayes normaux, équipés de l électrode sur la fenêtre ronde d une oreille (gauche), ont été soumis à des traumatismes sonores selon le schéma suivant

1) Au moins 20 jours après la mise en place de l électrode les réponses au clic et aux dif férents clics filtrés sont enregistrées.

2) Les cobayes sont alors exposés pendant 6 heures à un bruit blanc de 110 dB SPL (TS1 premier Traumatisme Sonore).

3) Pendant les 7 jours suivants, l évolution des réponses (récupération) est observée, en enregistrant les réponses au clic.

4) Les cobayes sont ensuite exposés de nou veau 5 jours de suite au même bruit blanc (6 heures, 110 dB) (TS2 à TS6). Ils sont testés chaque jour avant l exposition au bruit.

5) Les réponses au clic sont ensuite enregistrées régulièrement jusqu à ce qu elles cessent d evoluer (environ pendant un mois après le dernier traumatisme)

6) La veille du jour où chaque

sacrifié, on enregistre les réponses de l oreille équipée (gauche) pour l ensemble des stimulations (clic et clics filtrés)

7) Le lendemain l'oreille droite est testée de la même manière (électrode sur la fenêtre ronde) sous anesthésie générale.

8) L animal est ensuite sacrifié et les deux cochlées sont fixées après décapitation (glutaraldéhyde, tampon, acide osmique) Les cochléogrammes pour les oreilles droite et gauche sont alors réalisés en microscopie à contraste de phase (*surface preparations* Engström et al. 1964) sur des fragments des différents tours prélevés dans la moitié la plus accessible de la cochlée L autre moitié de la cochlée est incluse dans l'Epon pour observation ultérieure en microscopie électronique.

Nous ne rapportons ici que les résultats des cochléogrammes en contraste de phase, les observations en microscopie électronique étant en cours.

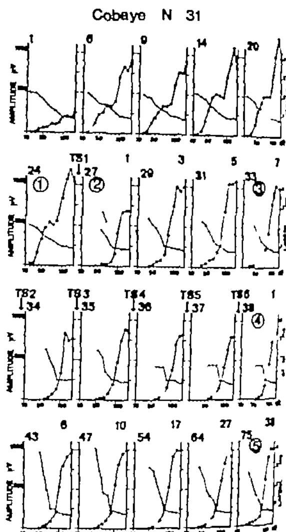


Fig 4 Evolution des réponses au clic (courbes entrée-sortie, amplitude-latence) chez le cobaye N° 31 Les chiffres en haut à gauche de chaque graphique expriment le nombre de jours après la mise en place de l'électrode sur la fenêtre ronde. Les chiffres en haut à droite expriment le nombre de jours après le dernier traumatisme sonore précédent. TS1 TS2 etc. traumatismes sonores successifs. Les chiffres cerclés *signalent les 5 étapes importantes dans l'expérimentation* *1* la veille du premier traumatisme (TS1) *2* le lendemain de TS1 *3* 7 jours après TS1. *4* le lendemain de TS6 *5* la veille du sacrifice, au moins 5 semaines après TS6.

RESULTATS

Tout d abord mentionnons que 3 cobayes normaux témoins, équipés de la même manière d une électrode à demeure sur la fenêtre ronde ont été simultanément observés 2 pen- des durées de 109 et 122 jours respective jusqu au sacrifice pour contrôle histo- que Les réponses sont restées, sur le plan des seuils, des formes et des courbes, identiques. Les cochléogrammes ont révélé des organes de Corti normaux à l exception du 4 tour ou quelques cellules ciliées externes étaient absentes, cela de la même manière pour les cochlées gauches (équipées en permanence de l'électrode) et droites (non concernées par l'approche chirurgicale de l oreille gauche ni par les stimulations sonores lors des différents enregistrements) Le 3 cobaye non encore sacrifié, présente, après plus de 6 mois, des réponses normales comme aux premiers jours.

Soulignons aussi que les enregistrements effectués le jour du sacrifice sur l oreille non équipée (droite) ont été chaque fois très comparables à ceux réalisés la veille pour l'oreille gauche chez l'animal éveillé On remarque seulement une légère élévation des seuils par rapport à ceux de l oreille gauche (due certainement à l'approche chirurgicale de l'oreille

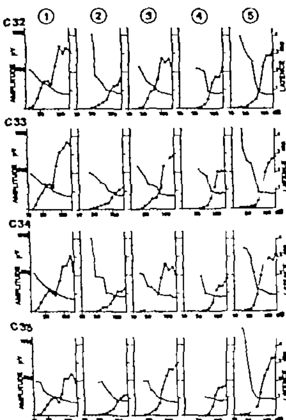


Fig. 5. Courbes entrée-sortie (Ch. non filtré) pour les autres cobayes, aux 5 étapes définies dans la figure 4.

juste avant les enregistrements) et une légère, mais constante, augmentation de la latence des réponses (dépendant de la profondeur de l anesthésie, comme on a pu le vérifier en observant les réponses à gauche sur animal anesthéné). Nous ne rapportons donc pas dans le détail les résultats des enregistrements effectués sur les oreilles droites, destinés essentiellement à contrôler la validité des observations faites sur les oreilles gauches. Par contre ces dernières sont présentées presque intégralement car outre leur intérêt dans le cadre de notre recherche elles permettent de montrer les possibilités de cette technique expérimentale qui devrait s avérer très pratique pour l'étude de nombreux phénomènes auditifs évolutifs.

Evolution des Réponses au Clic

Les réponses normales avant le premier traumatisme

Bien que les amplitudes des réponses puissent être d un cobaye à l'autre, assez différentes (certainement en fonction de la qualité des électrodes), les formes des réponses et des courbes entrée–sortie, amplitude–latence sont absolument comparables. Du seuil (autour de 20 dB peSPL) au maximum (130 dB peSPL) la latence varie progressivement de 2 msec à 0,8 msec; l amplitude augmente, avec l'intensité du clic, en deux étapes avec le plateau intermédiaire autour de 80 dB (Fig. 4 première rangée, Fig. 5-1) les différents pics N1 N2 etc. sont nettement visibles dans les formes des réponses dès le seuil (Fig. 6-1).

Effets du premier traumatisme sonore (TS1)

Le lendemain du premier traumatisme sonore on observe les modifications suivantes dans les réponses au clic (Fig. 4 5-2 et 6-2)

Le seuil (autour de 50 dB peSPL) s est élevé en moyenne de 30 dB.

La latence au voisinage du seuil, de l'ordre de 2 msec, est de ce fait plus élevée par rapport à sa valeur aux mêmes intensités avant le traumatisme il en est ainsi jusqu à 30 à 40 dB au dessus du seuil, au delà la latence est la même.

L amplitude augmente lentement jusqu à 80 dB puis plus rapidement au-delà, on n observe plus le plateau autour de 80 dB (forme « exponentielle » pour la courbe amplitude) au maximum (130 dB) l amplitude est réduite d'environ 50 %.

Les réponses sont considérablement élargies près du seuil et les pics N1 et N2 ne sont plus décelables.

Aux fortes intensités les pics négatifs sont nets mais précédés d'une déflexion positive importante. Celle-ci s observe également avant le traumatisme elle représente vraisemblablement le potentiel de sommation (positif car on enregistre au niveau de la rampe tympanique). Cependant le pic positif et la réponse

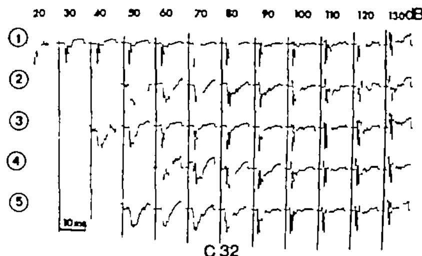


Fig 6 Formes des réponses au clic chez le cobaye N° 3 lors des 5 étapes définies dans la figure 4 sauf pour la dernière rangée qui correspond aux enregistrements effectués 17 jours au lieu de 39 après TS6. (Les tracés ont sensiblement la même dimension afin de comparer plus facilement entre elles les form des différentes réponses. Pour les amplitudes, se reporter aux courbes correspondantes sur la figu 5-cobaye 32, sauf pour la dernière rangée 5)

nerveuse ont tous les deux diminué après le traumatisme mais dans des proportions différentes.

Récupération après le premier traumatisme

Après 7 jours de récupération (Fig. 4 5-3 et 6-3)

Le seuil n est plus qu à 10 dB environ du seuil normal.

Les courbes entrée–sortie amplitude–la ne sont pas cependant redevenues nor faible amplitude et latence longue en ous de 80 dB Si trois cobayes présentent oujours des courbes amplitude « exponentielles » chez les deux autres (32 et 33) on observe la réapparition du plateau autour de 80 dB mais son amplitude est plus faible.

Aux fortes intensités l amplitude, la latence et la forme des réponses sont pratiquement les mêmes qu avant le traumatisme.

Près du seuil les formes des réponses sont cependant toujours larges (Fig. 6-3).

Effets des 5 traumatismes suivants (TS2 à TS6)

Le premier jour après les 5 traumatismes sonores successifs (Fig. 4 5-4 et 6-4) on note que

Le seuil n est que 10 dB environ au-dessu de ce qu il était le lendemain du premie traumatisme (60 à 70 dB)

La latence est toujours autour de 2 msec seuil (sauf pour le cobaye 35 où elle d emblée de 0,8 msec) Elle passe brutalem de 2 à 0,8 msec 30 dB au-dessus du seuil reste sensiblement constante jusqu à 130 dB.

L amplitude maximum est légèrement p grande qu après le premier traumatisme.

Les formes sont toujours larges près du se et paraissent normales au maximum. On marque, aux niveaux intermédiaires, l'appa tion progressive de N1 (Fig 6-4 à 70, 80 90 dB)

Evolution après le dernier traumatisme

Les réponses sont très caractéristiques et t semblables pour les 5 cobayes (Fig. 4 5-5 6-5) Elles sont pratiquement stabilisées vers 20e jour après le dernier traumatisme (Fig. 4 On note que

Le seuil se stabilise autour de 40 dB.

La latence est nettement plus longue pr du seuil (entre 3 et 4 msec) et elle décr rapidement jusqu à 80 dB ou elle reste co stante autour de 0,8 msec, cela dès les premie jours après TS6 (Fig 4)

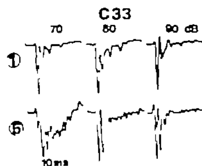


Fig. 7. Détail des réponses au clic chez le cobaye N° 33 en début *1* et à la fin *5* de l'expérimentation. Noter l'apparition progressive de N1 de 70 à 80 et 90 dB.

L amplitude est relativement très faible en dessous de 80 dB puis elle augmente très rapidement et est, à 130 dB, pratiquement la même qu avant les traumatismes.

Les formes sont toujours larges aux faibles intensités et apparemment normales au maximum. On observe encore très nettement l'apparition progressive du pic N1 précédent la réponse tardive large, lorsqu on augmente l'intensité du clic. (Fig. 6-5 et 7).

Réponses au clic et aux différents clics filtrés avant et après les traumatismes

Les réponses aux différents clics filtrés n ont été observées qu au début et à la fin de l ex périmentation (Fig. 8 et Tableau I).

Les réponses aux clics filtrés basse fréquence 1 000 et 2 000 Hz) ne sont pratiquement pas -- sur le plan des seuils, de l'amplitude de la latence

Par contre on note une très nette élévation des seuils pour les clics filtrés aigus 8 000 et 000 Hz.

La latence au seuil pour les clics filtrés aigus ., soit à 8 000 Hz, soit à 4 000 Hz, courte ≃ 1 msec). Ainsi, pour le cobaye 31 (Fig. 8) le seuil pour le clic filtré 8 000 Hz est passé 40 à 90 dB la latence de 2 à 1 msec et la ère partie de la courbe a disparue alors l'amplitude maximum à 130 dB est iden-ique Pour le clic filtré 4 000 Hz le seuil est ins modifié et on distingue dans les courbes amplitude-latence les deux segments distincts de part et d'autre de 90 dB On note encore de légères modifications pour le clic filtré 2 000 Hz et pratiquement aucune pour le 1 000 Hz.

La diminution du microphonique cochléaire sur les réponses au clic et aux clics filtrés, exprimée en dB sur le tableau 1 est faible. Elle est en général plus prononcée pour les clics filtrés 4 000 et 2 000 Hz.

Bilans histologiques

La proportion des cellules sensorielles détruites par rapport à l'ensemble des cellules ciliées est extrêmement faible. A titre d exemple les figures 9 et 10 montrent les cochléogrammes des deux oreilles du cobaye le moins atteint sur le plan là (N 31) et de celui qui présente le plus de destructions (N 33). Le tableau 1 exprime le nombre de cellules ciliées externes dé truites, en % du nombre total de cellules externes, pour les différents tours, chez les 5 cobayes. On remarque qu en moyenne les destructions se trouvent principalement au niveau du 2e tour Comme on pouvait s y at tendre, les cellules ciliées internes sont intactes

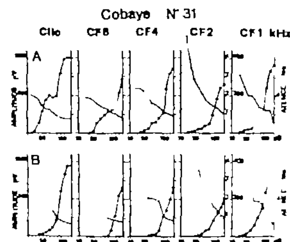


Fig. 8. Comparaison des courbes entrée-sortie pour le clic et les clics filtrés en début (*A*) et à la fin (*B*) de l'expérimentation chez le cobaye N° 31. Remarquer la similitude des courbes pour le clic et le clic filtré 8 000 Hz, en (*A*) avec celles d'un sujet humain normal (Fig. 1 gauche, pour le clic) et, en (*B*), avec celles d'un sujet présentant des réponses *dissociées* (Fig. 2 pour le clic et le clic filtré 8 000).

Tableau I. *Comparaison, pour les 5 cobayes des modifications du microphonique cochléaire (ΔMC perte en dB), et des seuils du potentiel d'action (ΔS.PA élévation du seuil en dB), pour le clic et les clics filtrés, avec les destructions de cellules ciliées externes (ΔCCE en % pour l'ensemble des tours (total) et aux différents tours (T1 T2 T3 et T4)*

ΔMC dB	Clic			8 kHz			4 kHz			2 kHz			1 kHz		
ΔS.PA dB		*Clic*			*8 kHz*			*4 kHz*			*2 kHz*			*1 kHz*	
ΔCCE (%)			Total			T1			T2			T3			T4
31	12,6	*20*	2,1	6,3	*50*	3,1	10,4	*20*	1,2	11,1	*20*	2,6	4 4	*0*	1
32	3,3	*15*	6,3	2,2	*20*	1 4	0,8	*50*	10,3	2,6	*30*	15,2	1,3	*0*	2
33	14	*10*	12,3	8,2	*50*	3,2	9 1	*50*	39 7	9 1	*30*	10	6	*10*	5
34	14	*20*	5,4	6,2	*40*	1,8	3,5	*30*	14,1	11,5	*30*	14,1	4,3	*0*	
35	9,5	*10*	9	9 1	*45*	6,5	11 1	*40*	8,7	10,1	*10*	10,9	4,6	*5*	9,_

(une seule cellule détruite sur l'ensemble des fragments examinés dans les 10 cochlées des 5 cobayes).

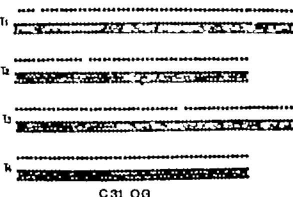
DISCUSSION

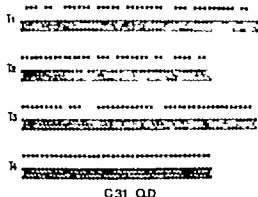
Si toutes les données expérimentales ont été décrites avec le plus de détails possible seules les caractéristiques les plus importantes seront discutées ici, en fonction de l objectif particulier de ce travail. En effet certaines particularités ne pourront être efficacement discutées que lorsqu on disposera de données en plus grand nombre et plus diversifiées à l occasion traitements oto-destructifs variés, en par ler plus sélectifs que le bruit blanc à large tre.

Tout d'abord soulignons que nos observations étaient principalement centrées sur les aspects et l évolution des formes des réponses et des courbes entrée–sortie, ainsi que sur les bilans anatomiques. La détermination des seuils du potentiel d'action et la mesure du microphonique cochléaire n ont pas été effectuées avec un souci de grande précision Etant donné d'autre part le caractère relativement modéré de l'aggression sonore et les faibles variations des seuils du potentiel d action et de l amplitude du microphonique, les résultats, en en qui concerne ces deux grandeurs, sont moins significatifs qu ils ne le seraient lors de traitements otodestructifs plus importants. Sur ces deux plans là on peut conclure cependant, en observant le tableau I que les modifications sont notables pour les clics filtrés 8 000 et 4 000 Hz, légères pour le 2 000 Hz et très faibles pour le 1 000. Cela impliquerait une atteinte préférentielle des premiers tours de la cochlée.

Sur le plan des formes des réponses et des courbes entrée-sortie les modifications sont beaucoup plus nettes et remarquablement comparables pour les 5 cobayes. On retrouve en outre toutes les caractéristiques des réponses « dissociées » décrites chez l'homme (Fig ?) Si on admet que les traumatismes sonores utilisés (bruit blanc à 110 dB) et leur répétition sont comparables à ce qui peut exister dans certains lieux de travail on peut admettre aussi que les mécanismes d'induction de ces modifications sont les mêmes dans notre expérimentation que chez l'homme présentant les réponses « dissociées » qui sont typiques ainsi que l'audiogramme, des surdités d'origine professionnelle.

Les lésions des cellules ciliées externes telles qu on peut les observer au microscope à contraste de phase apparaissent très modérées Bien que réparties sur l ensemble des tours elles sont prédominantes au niveau des ? et 3ᵉ tours, ce qui est en parfait agrément avec le contenu spectral du bruit blanc et les propriétés mécaniques de la membrane basilaire Le fait que ces lésions ne soient pas très

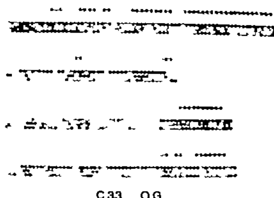


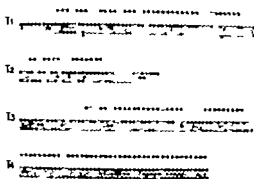


ig 9 Cochléogrammes des cochlées droite et gauche cobaye N° 31 Des 5 cobayes, celui-ci présente le moins de destructions cellulaires. ● cellule ciliée détruite.

localisées indiquerait en outre que les réponses « dissociées » apparaissent dès qu'il y a des ésions des cellules externes, quelle que soit eur localisation. Cependant le fait que les éponses soient altérées de la même manière orsque l'organe de Corti parait normal (cobaye 1 Fig. 9) que lorsqu'il est effectivement lésé cobaye 33 Fig. 10) suggère que ou bien des ellules ciliées apparemment normales (d'autant lus que le temps de récupération après le der ier traumatisme excède 1 mois) peuvent ne être fonctionnelles, ou bien que les lésions mitives se situent à un autre niveau (au eau des terminaisons nerveuses?), inaccesible au microscope à contraste de phase. in (1971) a décrit les différents niveaux s on pouvait effectivement observer au microscope électronique, des altérations immédiatement après le traumatisme sonore. Cependant pour des intensités de 110 dB pendant 2 heures, il ne note aucune modification. Il est certain que, dans notre expérimentation, la durée du premier traumatisme (6 heures), leur répétition et le délai respecté avant le sacrifice ont induit des modifications définitives.

Enfin il est intéressant de noter que, sur le plan des seuils comportementaux chez l'animal, on s accorde à trouver pas ou peu de modifica tions permanentes des seuils après traumatisme sonore modéré, avec cependant des altérations certaines des cellules ciliées externes (Ward & Duvall, 1971 Miller et al., 1971). Par contre nous trouvons, pour des lésions minimes, voire nulles, de l organe de Corti, une légère éléva-





g 10 Cochléogrammes des oreilles droite et gauche cobaye N 33 C'est celui qui présente, parmi les 5 cobayes, le plus de destructions cellulaires. ●, cellule ciliée détruite.

tion des seuils électrophysiologiques mais sur tout, et cela nous paraît le fait le plus important qui dépasse le seul problème de l audition liminaire, une modification nette et significative des formes des réponses et des courbes entrée-sortie Celles-ci impliquent une modification dans la synchronisation des fibres nerveuses et en conséquence dans la sensation auditive supra-liminaire.

SUMMARY

The first results are reported of a series of experiments designed to reproduce in the animal the different patterns of VIII nerve responses observed in human pathology Five guinea pigs with an electrode permanently implanted on the round window (left ear) are exposed to repeated acoustic trauma (6 times 110 dB white noise for 6 hours). VIII nerve responses to click and filtered clicks are followed before, during and after the acoustic traumas. Cochlear microphonic is also measured at the beginning and the end of the experiment. Five weeks (minimum) after the last acoustic trauma, control recordings are performed on the right ear before sacrifice and the right and left cochleas are observed by phase contrast microscopy (surface preparations). At the end of the experiment the VIII nerve responses are similar to the "dissociated" type of response observed in man in cases of occupational deafness. The organs of Corti range from normal to mildly injured at the level of the outer hair cells, mainly at the 2nd and 3rd turns.

ZUSAMMENFASSUNG

Die Resultate von Untersuchungen um beim Tier globale Wirkungen des Gehörnervs wieder zu erzeugen, vergleichbar den elektro-cochleographischen Wirkungen „dissociated" beim Menschen, liegen vor Meerschweinchen, welche mit einer Dauer Elektrode auf dem runden Fenster ausgestattet sind, wurden gemässigten ohrdestruktiven Behandlungen unterworfen (Klangverletzung). Die Antwort auf Klick (charakteristische Eingang-Ausgang- Weite-Lat[illegible] Formen) wird während und nach der Behandlung beobachtet. Das histologische Bild in der kontra[illegible] mikroskopischen Untersuchung wird besprochen [illegible] lässlich der elektro-physiologischen Angaben.

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ANALYSIS OF BONE REMODELLING IN THE OTOSCLEROTIC STAPES BY MEANS OF TETRACYCLINE LABELLING

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Abstract The distribution and the amount of bone tissue formed in the otosclerotic focus during 6 days were studied in 16 otosclerotic and 3 normal stapedes, by means of tetracycline labelling. The relative amount fluorescent new-formed bone was expressed as a ... age ratio NB/(NB+PB) of new bone (NB) on the pre-existing bone (PB). In the more active foci a layer of new-formed bone was noticed around nearly all the vascular cavities. In the less active and quiescent foci the new-formed bone was only noticed on the edge of some osteons. In the normal stapedes o trace of new-formed bone was observed.

ıne present investigation was undertaken to study the amount and distribution of the newly ..d bone in the otosclerotic focus, using ..cyclines as tracers. The observation by h et al. (1958) that tetracyclines become ıxed to bone matrix during its mineralization, enables us to distinguish the newly formed one from the pre-existing unlabelled bone. In ıe ground sections the newly formed bone is easily detected under ultraviolet (UV) light ıng to the yellow fluorescence of the tetracyclines. Part of this study was reported at the ..th Meeting of the Inner Ear Biology Group, ..d ın London September 1972.

MATERIAL AND METHOD

xteen stapedes removed during stapes surgery relief of a conductive deafness pre-operatively diagnosed as clinical otosclerosis were examined. Three normal stapedes removed from patients operated on by labyrinthectomy for Ménière's disease served as controls.

To all the subjects 900 mg demethylchlor tetracycline (Ledermycin) were orally administered for 5 successive days. With this dosage the tetracycline blood level was kept sufficiently high to allow an appreciable fixation to newly formed bone tissue during 6 days. The stapedes were removed 10 days after the last tetracycline administration. During this period of time the tetracycline completely disappears from the connective tissue while it remains in the newly formed bone tissue.

The stapedes were fixed in alcohol, dehydrated and embedded ın methacrylates. After polymerisation the specimens were ground by hand to a thickness of 40–50 μ The sections were photographed under UV light on colour reversal film (Ektachrome High Speed) using the Zeiss Ultraphot II microscope equipped with one or two energizing filters BG 12, and one barrier filter OG 50

On the colour diapositive of each section, the fluorescent new bone (NB) formed during the administration of the tracer the pre-existing unlabelled bone (PB), and the spaces not occupied by bone tissue were determined at the microscope by means of a Swift automatic point counter with a horizontal spacing of 1/20 mm and a vertical spacing of 1/6 mm.

..his research was supported partly by a grant from Consiglio Nazionale delle Ricerche and partly by a ..ant from "Ministero della Sanità

The values obtained were expressed as per centage ratio of NB/(NB+PB). This ratio ex pressed the volume of bone tissue which was being added per unit time (amount of bone formation) The values were reduced by 1/6 in order to obtain the amount of bone forma tion per day

The sections were microradiographed using a Machlett type AEG 50T X ray tube (7 8 kV 18 mA filter 1 mm Be) to check the mine ralization degree of the labelled areas.

RESULTS

Normal stapedes

No fluorescent newly formed bone was observed in any of the normal stapedes (Fig. 1 A) Only a faint green-yellow autofluorescence was present in the articular cartilage for the lenticular process of the incus, the cartilaginous layer of the footplate, the stapedius tendon and in some mucosal remnants (Fig. 1 A) This faint green yellow autofluorescence could easily be distinguished from the yellow fluorescence due to actual binding of tetracycline to bone tissue (Fig 1). Since the autofluorescence was observed in stapedes from cadavers without a clinical history of tetracycline treat ment it could be inferred that it was not elated to the administration of the drug.

We concluded that in the 3 normal stapedes he amount of bone formation per day was 0.0 (Table I).

Otosclerotic stapedes

In the normal areas of the sections of otosclerotic stapedes we never observed fluores cent newly formed bone A faint green-yellow autofluorescence was found in the same locations where it was demonstrated in normal stapedes (Fig. 1 B)

The otosclerotic foci were sub-divided into three groups according to their "activity" as indicated from the histological picture. This evaluation was based upon the dimensions of the marrow spaces, the number shape and dimension of the cavities and the characteristics of the bone matrix. A single stapes was inserted in more than one group when the foci with a different degree of activity were present

The more active foci showed a great amount of irregular vascular spaces, enclosed in a network of thin trabeculae consisting of "woven bone" The highest percentage of tetracycline labelling occurred in these foci (Figs. 2, 3) In one exceptional case all the surfaces were fluorescent and a diffuse fluorescence was also present inside the bone tissue. This condition prevented a precise determination of the amount of bone formation In 4 cases most of the surfaces were labelled with tetracycline (Figs. 2 B C, and 3) the percentage of labelling varied from 13 to 30% which means that the amount of bone formation per day ranged from 2.0 to 5 0% (Table II)

Table I *"Normal" stapedes*

No.	Side	Age (years)	Sex	NB (NB PB) per day
417	Left	57	♂	0 0
418	Left	18	♀	0 0
290	Right	33	♂	0 0

Table II *"Active" otosclerotic foci*

No	Side	Age (years)	Sex	Hearing loss (500, 1000, 2 000 Hz)	Evolution (years)	Tinnitus	NB (NB + PB) per day
414	Left	76	♂	45–45–50	4	Present	Very high, not measurable
422	Right	39	[illegible]	65–70–70	15	Present	5 0
431	Right	15	[illegible]	65–65–50	3	Present	2.8
432	Left	33	[illegible]	70–65–60	11	Present	2.6
167	Right	17		55–55–60	3	Present	2.4
429	Left	65	[illegible]	90–75–80	1	Absent	2.0

B



Fig. 1 (A) Micrograph under UV light of a normal stapes from an 18-year-old patient. (B) Otosclerotic stapes from a 25-year-old patient, photographed in the same conditions (22) and (C) at higher magnification (50). In the normal stapes a faint green-yellow autofluorescence is visible in the cartilage and connective tissue. No trace of fluorescent newly formed bone can be seen. In the otosclerotic stapes a bright yellow fluorescence marks the newly formed bone. Only in colour pictures (Fig. 1) can the yellow fluorescence due to tetracycline be distinguished from the autofluorescence in black and white pictures (Figs. 2, 3 4 and 5) this distinction is not possible.

Table III. "*Less active*" *otosclerotic foci*

No.	Side	Age (years)	Sex	Hearing loss (500, 1000, 2 000 Hz)	Evolution (years)	Tinnitus	NB (NB + PB) * per day
423	Right	38	♀	85–65–55	13	Present	2.2
422	Right	39	♀	65–70–70	15	Present	2.2
411	Right	46	♂	70–65–80	4	Present	2.2
4 1	Left	47	♀	70–75–95	17	Present	1.4
434	Right	35	♀	70–70–45			1.4
33	Right	57	♀	45–55–55	7	Present	1.3
427	Left	23	♀	50–50–50	5	Present	1.0
405	Right	25	♂	60–60–60	1	Absent	1.0

The less active foci showed less numerous and smaller vascular spaces (Figs. 1 B C, and 4) In some areas there was a tendency to a lamellar arrangement. A layer of labelled bone lined the wall of only some vascular spaces (Fig. 4). The thickness of this layer was not uniform. Therefore it was possible to distinguish in these foci the active surfaces undergoing calcification from the inactive surfaces of bone deposited prior to administration of tetracycline (Fig. 4 C). In the less active foci the daily amount of bone formation ranged from 1.0 to 2.2% (Table III).

In the quiescent foci the number and dimensions of the vascular spaces were markedly smaller Haversian systems could frequently be observed, but only a few were labelled with tetracycline (Fig. 5). The amount of bone formation per day was 0.2 to 0.4% (Table IV)

In most of the otosclerotic foci studied, the newly formed bone was observed inside the focus, seldom on the peripheral contour (Fig. ? C arrows)

DISCUSSION

Several investigators have attempted to study otosclerotic bone deposition by using tetracycline labelling. In 2 patients who had received tetracyclines, 1 year and, respectively 2 years prior to the operation, Frost (1962) observed the remodelling pattern of otosclerotic bone. The most noticeable findings, obtained by Alberti & Tarkannen (1963) using the same technique, were the presence of small amounts of fluorescent material both in the most active and in the most inactive foci. No fluorescence was evident in one normal foot plate.

Clarke's (1965) results on tetracycline-induced fluorescence seem to indicate that there *are differences depending on the stage of the disease* but his micrographs are questionable. Very little information was obtained with tetracycline labelling by Röckert et al. (1965) and by Crifò (1970). Garcia Ibañez (1966) observed traces of bone deposition in 27 out of 81 fragments of otosclerotic stapedes.

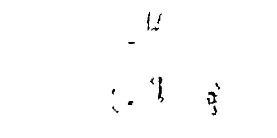
Our results confirm that in the normal stapedes there is no trace of newly formed bone. This observation is in agreement with the findings by Roberto & Morea (1972) who studied the post-fetal bone formation in the auditory ossicles of the dog by means of alizarine labelling. In the dog stapes, only deposition of primary bone tissue was observed and

Table IV "*Quiescent*" *otosclerotic foci*

No	Side	Age (years)	Sex	Hearing loss (500, 1000, 2 000 Hz)	Evolution (years)	Tinnitus	NB (NB + PB) * per day
413	Left	47	♂	80–85–70	12	Present	0.4
433	Right	39	♀	65–60–60	9	Present	0.3
405	Right	25	♂	60–60–60	1	Present	0.3
43	Left	33	[illegible]	70–65–60	[illegible]	Absent	0.2


A


B



it was completed within the third months of post-natal life. This means that bone remodelling does not take place in the stapes as in other parts of the skeleton.

All the otosclerotic foci showed a more or less active bone deposition which was massive in only one very active case where a high percentage of labelled bone was observed. Apart from this the bone formation rate per day ranged from 2.0 to 5.0% in the active foci, from 1.0 to 2.2% in the less active foci and from 0.2 to 0.4% in the inactive foci.

There is no doubt that the method employed by us only permits an approximate measurement of the amount of tetracycline-labelled bone Our data should be interpreted with caution also because they represent a 6-day exploration of a pathological process which evolves through many years.

The amount of bone formation per day in active otosclerosis seems high if we consider the long evolution of the disease and if we compare the figures obtained in otosclerosis with the data of the literature on normal and pathological bone Frost et al. (1960) and Frost (1961) obtained values of 0.01 to 0.02% in normal adult cortical bone and of 0.3 to 0.5% in ribs from young children. Values for the rate of bone formation in the Paget areas ranged from 0.1 to 0.6% per day while in the uninvolved areas they were from 0.04 to 0.1% (Sissons & Lee, 1964). An increased bone formation rate was observed in hyperparathyroidism by v. der Sluys Veer et al. (1964) and in 2 children suffering from osteogenesis imperfecta (from 0.30 to 0.42% per day) by Lee (1965).

Absence of labelled periosteal bone was noted in most of the otosclerotic foci examined by us. This means that the otosclerotic foci undergo an internal remodelling also when their overall size does not increase. In one case we observed a periosteal deposition in the area adjacent to a blood vessel (Fig. 2 C) and this can give an idea of the way the focus increased its size.

The distribution of labelled bone was not uniform inside the same focus, i.e., some areas are more active others less active or quiescent.

It was not possible to find a correlation between the amount of bone deposition and clinical data (see Tables II, III IV) With regard to the age it can be noticed that the 2 younger patients (15 and 17 years old) belong to the group of high bone deposition rate the same group, however comprises a patient 65 years old. Relatively young patients showed a low deposition rate. Regarding the duration of the otosclerotic process, 4 recent cases and 2 with a long clinical story belong to the group with very active foci 3 other cases with a long evolution showed quiescent foci. No relationship could be established between bone deposition rate and hearing loss or tinnitus.

In Spain, stapedectomies were carried out by L. Garcia Ibañez and in Italy by E. Bocca and S. Furato

ACKNOWLEDGMENT

We would like to express our thanks to Professor R. Amprino and Professor G. Marotti for their cooperation.

RESUME

Par la technique de marquage avec la tétracycline on a analysé la distribution et la quantité du tissu osseux se déposant au cours de 6 jours de traitement dans 16 étriers otosclérotiques et 3 étriers normaux. La quantité relative de tissu osseux formé au cours du traitement par le fluorochrome a été indiquée par le rapport pour cent entre l'os nouveau (ON) et l'os pré-existant (OP), soit ON/(ON + OP). Dans les coupes des foyers les plus actifs une bande de tissu osseux récemment formé tapisse la paroi de presque toutes

Fig. 2 Otosclerotic stapes from a 65-year-old patient. The distribution and the amount of the newly formed bone labelled with tetracycline is detected under UV light. Almost all the vascular spaces are lined with fluorescent bone. The autofluorescence of the cartilage and of the stapedius tendon cannot be distinguished from the true fluorescence in a black and white picture. A (22); inset is shown at higher magnification in B (65) and C (130). The picture in (B) was taken with two, and that in (C) with one energizing filter to show that tetracycline labels the bone and not the connective tissue.

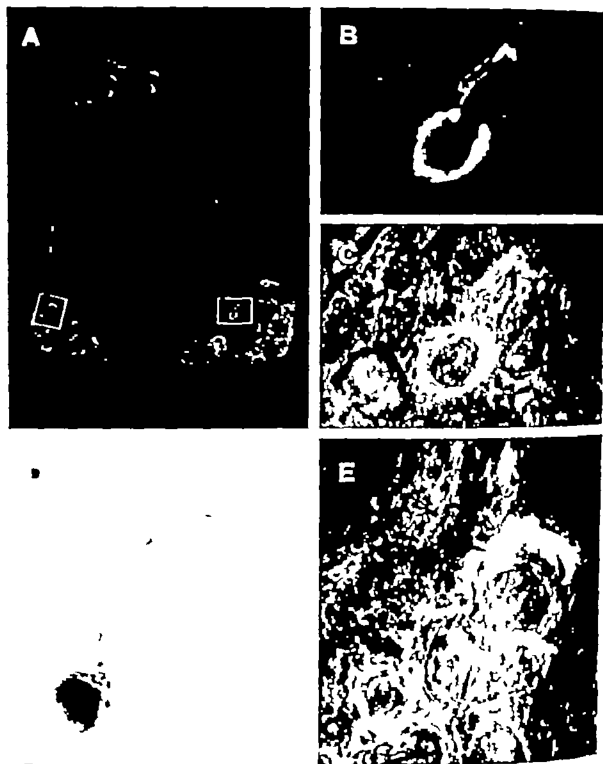
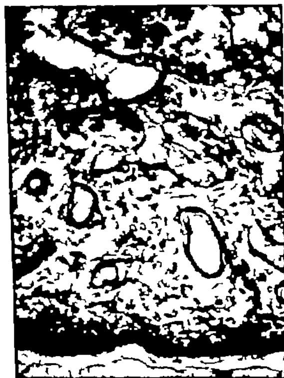


Fig 3 Otosclerotic stapes from a 15-year-old patient. "Active" otosclerosis like that shown in Fig. _ (A, 22, B and C, 195 D and E, 43.) The pictures (C) and (E) were taken with one exposure [illegible] show the structure of the labelled bone and the surrounding area. Micrographs obtained under UV [illegible]







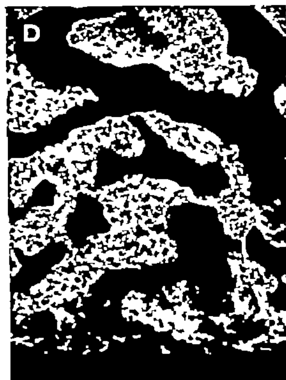


Fig. 4. Otosclerotic stapes from a 25 year-old patient. The disease is "less active" than in the cases shown in Figs. 2 and 3. (A) The otosclerotic focus involves the whole footplate, but only a small part is labelled with tetracycline (inset). This is shown at × 190 in (B) (2 energizing filters); (C) (1 energizing filter); and (D) (microradiograph). In (C) it is possible to distinguish the active surface undergoing calcification from the inactive surfaces and (D) shows the low mineral content of the newly formed bone.





Fig 5 Micrograph under UV light of two otosclerotic stapedes from patients 39 years (A) and 33 years old (B) (×22). The foci are quiescent and only a fe[w] vascular spaces are lined with newly formed bo[ne]

[le]s cavités vasculaires, tandis que dans les foyers moins actifs ou quiescents la bande d os néoformé longe seul la lumière de quelques ostéones. On ne trouve pas trace de néodéposition osseuse dans les étriers nor maux.

ZUSAMMENFASSUNG

Die Verteilung und die Menge des Knochengewebes das in dem otosklerotischem Herd in 6 Tagen ge macht wurde wurde untersucht in 16 otosklerotischen und 3 nicht-otosklerotischen Steigbügeln, mittels Tetra cyclin Markierung. Die relative Menge von fluoreszierenden neu-hergestellten Knochen ist in einer prozentualen Ration NK (NK + VK) von neuen Knochen (NK) im Gegensatz zu den vorherigen Knochen (VK) ermittelt worden. In den meisten aktiven Herden wurde eine Schicht von neu-hergestellten Knochen fast um all die in dem Hohlraum befindlichen Blut gefassen vorgefunden. In den weniger aktiven und ruhenden Herden wurde der neu-hergestellte Knochen nur um den Rand von einigen Osteonen vorgefunden. In den normalen Steigbügeln wurden keine Spuren von neuhergestellten Knochen entdeckt.

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DISCUSSION

G Zechner We hope to show where tetracyclin is thought to go We think that the depolymerized acid mucopolysaccharides are the substances which bind the tetracyclin. Those mucopolysaccharides are fairly dense in active otosclerotic foci. These facts we showed by means of coloured slides of post-mortem specimen. They agreed exactly with Dr Iurato's findings.

H Engström. The activity of otosclerosis may vary in different areas. One single section through the centre of the stapes may give incomplete information of the stapes as a whole. It would therefore be better to section the footplate "horizontally" and I do believe it is possible to make many sections with the aid of a diamond or special steel knife. I must also congratulate Dr Zechner on his beautiful material, presented in the discussion. It was, however evident that it was not from the stapes alone.

S Iurato (Reply) to Mr *Engström.* It is really a pity that the diamond saw has a thickness of 300 μ preventing a serial sectioning of the footplate. At maximum, only a few sections can be obtained from a whole footplate.

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CLINICAL SIGNIFICANCE AND DIAGNOSTIC VALUE OF AUDITORY BONE THRESHOLD

Some Critical Considerations

O Sala

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Abstract The author surveys the main conditions which lead to a variation of the BC auditory threshold, although lesions of the sensorineural inner ear epithelium may not be shown. The author's criticism of the value commonly assigned to BC threshold impairments is also supported by the results yielded by a scheme of medical therapy in some cases of sensorineural deafness, even lasting since more than . years before the treatment. It ensues that a BC threshold elevation should not be considered, as a rule, the expression of an irreversible damage of the inner ear sensory cells. The argument, which holds practical implications mainly from a diagnostic and surgical standpoint, is still the object of experimental and clinical research.

The precise determination of auditory bone conduction (BC) threshold is commonly thought to represent an essential diagnostic clue both in clinical Audiology and Ear Surgery. Several reports on this subject have been published which treat in depth either the methods employed in determining the BC threshold in both normal and pathological conditions, or the difficulties arising from BC masking in asymmetrical hypoacusis.

As a rule, BC threshold is assumed as being the sole and true expression of the anatomical and functional features of the inner ear structures and its elevation would represent the very symptom of an unavoidable and irreversible impairment of the inner ear. A critical review of the most recent literature and also some favourable results yielded by a scheme of medical therapy we designed and used in cases of chronic sensorineural deafness led us to question the semiotic and clinical value generally ascribed to the BC threshold.

As a matter of fact, an elevation of BC auditory threshold may have *extra-labyrinthine origins*. Let us remember for instance: (*a*) the false labyrinthisation due to the simultaneous blockade of both the oval and round window (Bocca et al., 1968) the inner ear temporary overloading which may be observed either in otosclerotic patients (Carhart's notch) or immediately following a stapedectomy if non-biological prostheses were used (e.g. gelfoam, as we showed by automatic audiometry: Sala & Babighian, 1971) or after a tympanoplasty. Moreover both the AC and BC threshold elevation may be observed when the VIII nerve *is impaired (neuromas, tumors of the cerebello-*pontine angle) or when cochlear nuclei are somewhat damaged (Fisch 1970).

The BC threshold elevation of *labyrinthine origin* is related to a degenerative involvement of the inner and outer hair-cells. This involvement may be either primitive, or may ensue from some alteration taking place in the supporting structures of the inner ear or in the labyrinthine fluids (Borghesan 1955 Bosher 1970). Furthermore, there exist other pathological conditions (some of them already well known) which may lead to a BC threshold elevation, although damage to the organ of Corti may not be demonstrated. And namely (I) vascular stria atrophy (mainly at the apical

turn of the cochlea) (ii) cystic degeneration of the spiral ligament (either at the middle or the apical turn) (iii) primary neural de generation of the spiral ganglion cells (iv) basilar membrane stiffness, which is followed by a conductive cochlear impairment. This basilar membrane stiffness accounts for some audiological pictures of presbyacusis (Schuknecht, 1970· Kerr 1969) and for hypoacusis caused by an endolymphatic hydrops in the initial phases of Menière s disease (Tonndorf 1968).

Each of the four above-mentioned conditions will produce a symmetrical elevation of both the BC and AC threshold, whether or not a damage of the sensorineural epithelium is demonstrable. From an *experimental standpoint* let us remember some recent data. Pre liminary studies on the temporary auditory fatigue (TTS), performed by Babighian et al. (1972) with electrophysiological techniques, showed that following intense and prolonged sound stimuli, a peculiar involvement of the superior centers may occur which is added to the peripheral effects of fatigue.

That the higher levels of the auditory system may electrically behave in a different way than the receptor with regard to the same sound stimulus, was similarly shown by Suga & Schlegel (1972), and by Marsh et al. (1961) and Humphrey & Buchwald (1972) mainly in re search on habituation. In other words, there is some experimental evidence that an auditory phenomenon which displays a peripheral origin at the audiometric testing may imply central components.

Moreover marked discrepancies were demonstrated between sensorineural hypoacusis and *its histological picture. For instance, in* cases of permanent auditory fatigue (PTS) electron microscopy studies showed the cell damage at the organ of Corti to be quite dispropor tionate when contrasted with the audiometric picture (Ward, 1972)

Other elements also support our critical attitude toward the whole problem of BC threshold evaluation.

Spontaneous variations of the BC threshold may be observed in the first phases of Menière s disease (generally accompanying a ver tigo attack) in sudden deafness of a viral origin, in sensorineural hypoacusis produced by congenital syphilis (Hahn et al., 1962) in some ototoxic hypoacusis, caused either by salicylate (Myers & Bernstein, 1965), or by quinine (Falbe Hansen, 1941) and in the initial phases of noise-induced hearing loss (Rüedi, 1954). Those threshold variations are likely to be related to biochemical disorders of the ear rather than to sensory cell degeneration.

BC threshold may also vary following *medical or surgical treatment* In patients treated by *medical therapy* an improvement of BC threshold has been observed in the following cases: in the initial Menière s disease (Beretta & Livan, 1956 De Vincentiis et al. 1964 Gnecal et al., 1968, Klockhoff & Lindblom 1968) in the "idiopathic" sudden deafness (Bosatra & De Stefani, 1963) in sensorineural hearing losses caused by a post-stapedectomy labyrinthitis (Causse et al., 1971), in some hypoacusis provoked by ototoxic drugs, congenital syphilis, thyroid diseases, collagen diseases (Cody 1971).

Finally we would like to mention some favourable results, yielded by the scheme of medical therapy we devised, which has been applied, throughout 1971 in 70 patients suffer *ing from sensorineural hearing loss of various* origin (chronic Menière s disease, ototoxicity haemolitic disease skull injury noise-induced hearing loss, etc.).

As a matter of fact, this scheme hinges on vasodilator drugs, mannitol, heparine, and ACTH anti-bradiquinine, anti-serotonine and tissue-oxygenizing drugs are used too The therapy lasts about 2–3 weeks it will be pur sued at home, throughout 2–3 months, at a reduced dosage. Research upon the action mechanisms of these drugs on the inner ear has been done in our clinic and is still being performed. some data, which show a t pharmacological action on the sen l and/or supporting structures, and se-

quence a variation of both the AC and BC threshold deserve to be shortly reported.

Automatic audiometry performed immediately before and after mannitol i.v. perfusion showed, in some cases of "chronic" sensorineural deafness, both an improvement of the threshold and a narrowing of the "C" tracing amplitude. In some instances, this phenomenon was strictly dependent on the duration of the perfusion. As a rule these cases showed, at the end of therapy an improvement of both the tonal and vocal threshold, and higher SISI scores than before the treatment (Babighian 1972). Similar DL variations, clearly dependent on mannitol administration, were demonstrated by means of an electrical device which allows to record the stapedial reflex "modulation" amplitude (Babighian & Colletti, 1972). The reflex is elicited by an intense sound and the superimposition of intensity modulated acoustic stimuli. By this technique an objective evaluation of DL changes may be obtained.

The patients we dealt with suffered from a "chronic" sensorineural hearing loss. In addition to amelioration in cases of nuclear deafness and of unknown origin dramatic improvements were observed in some cases of Menière's disease, originating more than 2 years earlier. These cases displayed either a flat or a descending audiometric curve, already stationary, the supraliminal tests being clearly positive.

Details of both the treatment and the results have been given in previous papers (Sala 1971, Sala & Babighian, 1971, 1972); nevertheless, we would like to point out that these unhoped-for results led us to review critically the problems related both to BC auditory threshold measurements and significance, and to its *topo-diagnostic and clinical value*.

Improvements of BC threshold have been reported following *surgery* in cases of Menière's disease (Arslan, 1969; Cody 1971; House, 1962), and in decompressive interventions on the cerebellopontine angle (Baker & Christoferson, 1950).

In view of our data, one must therefore be wary about considering the BC threshold as the expression of an irreversible histofunctional impairment of the sensorineural cells. As a matter of fact, the BC threshold elevation may derive from several different inner-ear extralabyrinthine, or perhaps, even nuclear factors, which sometimes may be improved by appropriate medical treatment. The latter also has implications from the pre- and post-surgery standpoint, when we are dealing with patients who need "functional" intervention in the middle ear.

RESUME

L'auteur, dans une synthèse critique, prend en considération les conditions qui amènent à une modification du seuil auditif en CO, sans que des lésions de l'épithelium neurosensoriel cochléaire puissent être demontrées. Objet de la critique de l'auteur est l'opinion, commune à la plupart des otologistes, que le seuil en CO soit l'expression fidèle des conditions anatomofonctionnelles des éléments neurosensoriels de l'oreille interne, et que son aggravation soit l'expression d'un dommage cochléaire irreversible. Des résultats favorables, obtenus par un schéma personnel de thérapie médicale chez des sujets souffrant par une surdité neurosensorielle « chronique », semblent confirmer cette attitude critique.

L'argument, qui presente des implications d'ordre pratique (surtout au point de vue diagnostique et chirurgical), est encore, à present, objet de recherches *experimentales et cliniques*.

ZUSAMMENFASSUNG

In einer kritischen Synthese berichtet Verf. über die Faktoren, die eine Veränderung der CO-Hörschwelle hervorrufen, ohne dass es möglich ist, irgendwelche Schädigungen am neurosensoriellen Schneckenepithel nachzuweisen. Das Objekt der kritischen Betrachtungen seitens des Verf. ist die allgemein bei Otologen verbreitete Meinung, dass die CO-Schwelle den exakten Ausdruck der anatomischen und funktionellen Zustände der neurosensoriellen Komponenten des Innenohrs darstellt und dass Verschlechterungen als Anzeichen einer irreversiblen Schädigung aufzufassen sind. Einige günstige Resultate, die mit einem persönlich ausgearbeiteten medikamentösen Behandlungsschema bei Patienten mit „chronischer" neurosensorieller Schwerhörigkeit erzielt werden konnten, scheinen diese kritische Einstellung zu rechtfertigen. Dem Thema, das auch praktische Probleme umfasst (besonders in diagnostischer und chirurgischer Hinsicht), werden augenblicklich noch experimentelle und klinische Forschungen gewidmet.

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INFLUENCE OF EXPERIMENTAL HYPOTHYREOSIS ON THE INNER EAR IN RATS

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Abstract Experimental hypothyreosis was induced in four generations of rats. The temporal bones of the fourth generation were prepared for histological studies and the changes in the inner ear are now presented.

This paper is the continuation of the research work undertaken by Gušić and his co-workers in Yugoslavia in the regions where endemic goitres prevail. Clinical studies were made of the changes in the cochleovestibular apparatus of people with endemic goitres. In one of his works Gušić said that "all signs indicating multiple lesions in the region of the central nervous system could be established as the cause of cochleovestibular disorders and not changes in the area of the temporal bone" Such a result of the clinical investigations is not entirely in agreement with the histological findings in temporal bones described in cretins and even in cretinoid dogs by many authors (Alexander 1908 Nager 1917 Manasse, 1909).

This difference promped us to study the changes in labyrinths of hypothyreotic rats. The course of the experiment was prompted by the opinion that changes in the central nervous system and in the process of ossification occur very early during the period of intra uterine development of a child whose mother has an endemic goitre. Therefore the hypothyreosis was experimentally induced during the intra-uterine development and continued postnatally until the animals were sacrified.

The experiment was started with 10 healthy female rats of 3 months, weighing 210–250 g. These animals were fed with the standard food to which 0 2 g of Propylthyouracil (PTU-Propocyl Rhenania, Kali-Chemie, Hannover) was added per 100 g. Accordingly the individual daily dosis was about 25 mg After such treatment over a period of 3 weeks we permitted fertilization. The male rats lived under the same conditions but were fed with standard food only The fertilized female rats were treated throughout the period of gestation with PTU and this treatment was continued after they had had their litter The male off spring were removed and the females treated with PTU until they became sexually mature. Fertilization was again permitted by normally fed male rats. After fertilization this first generation was again treated throughout the gestation period with PTU and this was continued even after they had had their young. The experiment was repeated until the fourth generation when we obtained as offspring animals which at the age of 3 months weighed about 40–60 g, had a scanty hairy coat and sluggish movements. This generation was sacrificed and intravital fixation was undertaken. The head was removed and prepared for histological examination.

The second group of animals served for control purposes. These were animals which after birth were immediately put on the previously described treatment with Propyl-

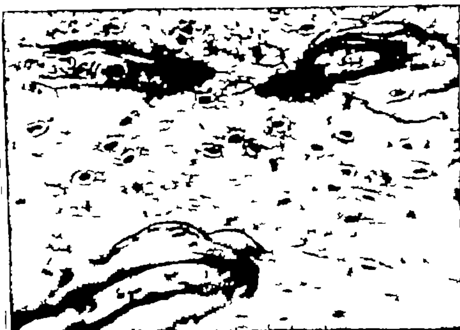


Fig 1



Fig 2

Fig 1 A typical structure of the labyrinthine bony capsule

Fig 2 Cartilaginous islands in the bony capsule of the labyrinth.

thyouracil together with their mothers. These animals were also sacrificed when they completed 3 months of life.

The third group of animals also serving as control group consisted of animals fed normally without having been submitted to treatment.

The histological analysis of the labyrinth in animals of the first group showed that the sensory cells in the labyrinth and the ganglial cells were normal in their appearance and number The bone of the labyrinthine capsule did not show the typical lamellar structure the cellular elements were multiplied as also were the blood vessels (Fig. 1). Cartilaginous tissue remained here and there, especially in



Fig 3 Discontinuity of the epithelium in the region of the prominentia spiralis with the migration of the cells into the ductus cochlearis.

the endosteal layer (Fig. 2) We should like to mention changes in the region of the prominentia spiralis which we were able to establish in each animal of the first group. A discontinuity of the epithelium with migration of the into the ductus cochlearis was involved here (Fig. 3)

For the time being the interpretation of this finding is purely speculative. The finding of cartilaginous islands in the bony capsule of the labyrinth has sometimes been seen in rats without any treatment or disease.

In animals of the second and the third group the previously mentioned changes could not be established. The findings were entirely normal.

RÉSUMÉ

Les os temporaux de la quatrième génération de rats hypothyréotiques ont été examinés histologiquement. Les altérations dans l oreille interne sont décrits.

ZUSAMMENFASSUNG

In Ratten wurde eine experimentelle Hypothyreose durch vier Generationen erhalten. Die Schlafenbeine der vierten Generation wurden für histologische Untersuchung vorbereitet und die Veränderungen im Innenohr werden praesentiert.

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FREEZE DRIED BONE AS A MEATAL IMPLANT

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Abstract. As part of a programme to improve the operative results in surgery for congenital meatal atresia, we have studied the fate of freeze-dried homograft bone in dogs when implanted as an isotopic graft. Histological studies were made of the graft reaction at regular intervals up to 2 years. Osteogenic activity was monitored by tetracycline fluoroscopy Regional lymph nodes were examined for evidence of graft rejection. There was no homograft reaction and the graft acted as a scaffold for new bone formation.

Most otologists will agree that the commonest complication of operations for congenital atresia of the ear is that of stenosis of the newly fashioned meatus. Indeed, this was found in approximately 23% of 181 operations performed in the Radcliffe Infirmary Oxford, since 1958. In an attempt to overcome this problem it was decided to examine the possible value of a two-stage procedure in which the first step would consist of burying a bony homograft meatus in situ and closing the skin completely over it.

The present paper is an account of the findings obtained in dogs subjected to the first stage

MATERIAL AND METHOD

The graft consisted of bony meatus alone with no soft tissue attached. Grafts were taken under clean but not sterile conditions from cadaver heads which had been refrigerated at 2 C for 48 hours following sacrifice.

Sterilisation was achieved by immersion in 2 ethylene oxide for 12 hours. Ethylene oxide is a highly volatile fluid which boils at 10.7 C and sterilisation was carried out in a fume cabinet at 4 C. Aerobic and anaerobic cultures from the grafts and containers showed no growth on nutrient broth or Robertson s meat medium, and there were no wound infections in the experimental animals. Following sterilisation the grafts were placed in Pyrex glass containers and snap frozen to −79 C in a mixture of dry ice and ethyl alcohol prior to freeze drying in a conventional freeze drying apparatus. Drying was completed when the vacuum pump reached 0.01 mmHg indicating that sublimation of water vapour from the graft had ceased (Fig. 1).

The grafts were then stored under vacuum and reconstituted with normal saline before implantation.

The hosts were male dogs aged 6 months to 2 years and litter mates were not used as donors and hosts. After excision of the pinna the outer portion of the host meatus was enlarged to accept the graft, which was wedged into position after suitable trimming with a cutting burr

The graft reaction was studied at regular intervals up to 2 years. The meatuses and surrounding bone were decalcified in 5% nitric acid, paraffin embedded and sectioned in the sagittal plane. Tetracycline-labelled specimens were embedded in plastic, and sections viewed under ultraviolet light. Lymph nodes from both sides of the neck were examined for evidence of an immune response.

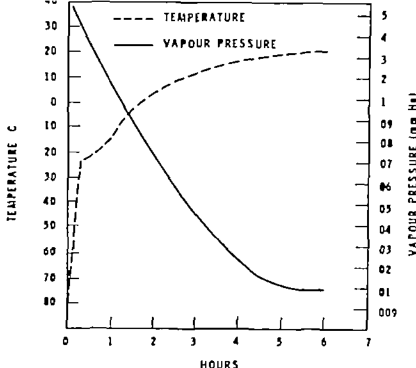


Fig 1 Graph of average dry
time for grafts of between 3
4 G undried weight. Vapour
sure was measured with a Pi
vacuum gauge.

RESULTS

During the first month there was consider
activity at the surfaces of the graft and l
which were separated by a layer of granula
tissue apart from small pressure points wh
the graft had been wedged into position (F
2) The host surface showed evidence of ost
genic activity with new woven or non-lamel
bone growth into the granulation tissue (F
3)

This process was further advanced at
months and active osteoblasts lined the ho
surface. The graft showed early attack l
multinuclear osteoblasts with numerous Ho
ship s lacunae, but this did not appear
persist. At 2 months the graft surface show
little activity There was no evidence of ne
bone formation at this stage Lymph nod
examined at 2 months showed reactive hyper
plasia only

The 3-month and 16-month sections show
new bone formation on the surface of th
graft, both in the intrameatal and free oste

Fig 2 Low-power view to show free portion of graf
in relation to host bone. The graft lumen contai
gelfoam, though in subsequent human patients
polythene obturator was used.

Fig. 3 Surface of host bone showing marked osteogenic activity with new woven bone formation occurring in the adjacent granulation tissue.

Fig. 4 Three-month graft consisting mainly of dead bone but new layer of living host bone lines the graft surface.

Fig 5 Body of 6-month graft showing an island of new bone formation around a vascular channel.



Fig 6 Tetracycline-labelled new bone seen on the graft surface of a section taken at 3 months.

Fig. 7. Polarised light view of graft-host fusion at 1 year showing interweaving of bone collagen.

portions (Fig. 4). Small islands of new bone were seen in the body of the graft, surrounding the vascular channels with cement lines radiating from them (Fig. 5). The graft host junction was recognised by the firm apposition of living and dead bone. Tetracycline-labelled new bone was seen on the surface of the graft when sections were viewed under UV light (Fig. 6).

The 1 year and 2 year sections showed a continuous process of graft fusion with host bone. Polarised light examination revealed intermingling of graft and host bone collagen (Fig. 7). The graft underwent a process of creeping substitution, that is, gradual replacement of dead by living bone. At 2 years it remained as a firm bony meatus with new bone lamellae surrounding residual islands of dead bone (Fig. 8).

CONCLUSION

As a result of these experiments in dogs it was felt justifiable to use a similar method in human patients. Although the patients were children, an adult size meatus was implanted; this was done in the same way as the dog experiments. The first patient had the first stage

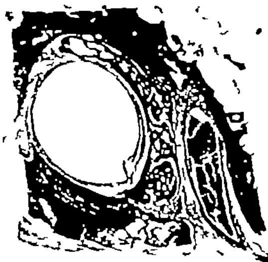


Fig. 8. Two-year graft showing a firm bony meatus of good thickness. Scattered islands of dead bone were still present in the body of the graft.

done in May 1970 Her second stage was performed a year later at which the obturator was removed, the meatus Thiersch grafted, and local flaps fashioned the line the meatal entrance. The meatus remains stable and of good size We believe that homograft meatuses can be used to advantage in certain patients with congenital atresia, and it is planned to report at a later stage on our patients who have received homograft meatuses.

RÉSUMÉ

Dans le cadre d'une étude expérimentale dont le but était d'améliorer les résultats du traitement chirurgical des atrésies congénitales du conduit auditif externe, nous avons examiné le sort d'homogreffes osseuses autotopiques hypophylisées chez le chien. La réaction des greffes fut suivie par des contrôles histologiques effectués à intervalles reguliers pendant une durée de 2 ans. L activité ostéogenique fut mesurée par fluoroscopie à la tétracycline. Les glandes lymphatiques régionales furent examinées afin d'y mettre en évidence des signes de rejet. Il n y a pas eu de réaction aux homogreffes, les greffons servant de support à l'ostéoneogenèse.

ZUSAMMENFASSUNG

Als Teil eines Programmes zur Verbesserung der chirurgischen Ergebnisse in der Behandlung kongenitaler Atresien des äusseren Gehörorganes, wurde das Los gefroren-getrockneter autotopischen homogenen Knochentransplantaten in Hunden studiert. Histologische Untersuchungen der Transplantaten wurden in regelmässigen Abständen während 2 Jahren ausgeführt. Die osteogenetische Aktivität wurde mittels Tetracyclin-Fluoroskopie ausgemessen. Regionäre Lymphknoten wurden für Zeichen von Ausstossen der Transplantaten untersucht. Es war keine Reaktion zu den homogenen Transplantaten vorhanden, und die Transplantaten dienten als Rahmen für die Knochenneubildung.

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DISCUSSION

W F House: (1) Why use polyethylene dioxide and freeze drying instead of 70% alcohol which has been found satisfactory in homograft ossicles? (2) Do the grafts line well with skin or does stenosis occur from granulation in the lumen of the grafted external canal?

I Friedmann Aseptic new bone formation in this interesting experiment is of great importance. Is the newly formed bone originating in the bulla or the external auditory meatus? What has happened to the squamous epithelium of the meatus? Could the new bone formation lead to the formation of exostoses or the complete osseous obliteration of the lumen?

J L. W Wright (Reply) to Mr *House* and Mr *Friedmann.* Work by Burwell and others has shown that freeze-dried bone will foster new bone formation whereas boiled, methiolated and deproteinized bone does not. That is, the former seems to encourage osteoblast formation by release of bone inductor from the organic substrate.

Woodruff has also stated that freeze drying is the most effective way to impair the antigenicity of large bone grafts. Our human grafts are considerably larger than incus bones and we thought therefore that this was an important factor

The grafts were implanted with a small polythene obturator which stimulated an early well differentiated fibrous bed, thus reducing the number of undifferentiated connective tissue cells available to stick the graft surface. In dogs we noticed that middle ear epithelium grew out to line the meatus, which showed no tendency to exostosis formation during the period of study In human patients we have implanted the meatuses as part of a two-stage procedure. At the second stage, 9 months later the meatus was found to be lined with a thin layer of fibrous tissue which was suitable for a Thiersch graft. The middle ear mucosa had closed off the middle ear space, forming the medial layer of a future tympanic membrane.

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SYMMETRICAL HEARING LOSS IN BRAIN STEM LESIONS

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Abstract. An examination of bilateral deafness resulting from proven lesions of the brain stem has shown that the pure tone audiograms at the two ears are invariably identical. This finding has interesting theoretical implications concerning the tonotopic organisation of the auditory pathways in the brain stem which will be discussed.

Certain facts about the clinical effects of lesions of the central pathways of the cochlea are well known. Thus, for example removal of one cerebral hemisphere in animals has only a trifling effect upon hearing as judged by the pure tone audiogram and indeed we ourselves have been unable to detect any significant difference in the hearing level at the two ears of patients subjected to hemispherectomy

The explanation of this seems to be that above the level of the cochlear nuclei there is a substantial division of the cochlear pathways as shown in Fig. 1 so that the surviving hemisphere remains supplied with impulses from both cochleae.

Now this argument may well be applied to a unilateral lesion at any point above the decussation and it follows therefore that a unilateral retro-cochlear hearing loss can only result from a lesion of the cochlear nuclei on one side or the nerve fibres peripheral to them but not from more central unilateral lesions.

By the same token a brain stem lesion above the level of the cochlear nuclei can only give rise to deafness if it involves the cochlear pathways bilaterally and in this event there should be deafness at both ears. We know however from the work of Rose et al. (1960, 1963) and others that there is present in the brain stem a tonotopic organisation of the auditory fibres at all levels.

Adopting the same argument as before this leads to interesting speculation concerning the character of the hearing loss at the two ears since it may be presumed that central bilateral deafness can only occur when fibres subserving identical frequency bands on both sides of the brain stem are involved. In this event bilateral deafness will result which must of necessity be symmetrical in respect of its frequency distribution at the two ears.

This is illustrated schematically in Fig. 2 in which are shown the two central cochlear pathways left and right within the brain stem each with its tonotopic arrangement of fibres. The enclosed areas on each side represent lesions resulting for example from plaques due to multiple sclerosis. Although as will be seen the involvement on one side is considerable, deafness can only result from those frequency regions which are common to both sides indicated by the solid shading

With these considerations in mind we have reviewed some 500 patients with brain stem lesions who have been examined in the Neuro-otological Clinic at Queen Square, London. As was to be expected deafness was not a common finding nevertheless in those patients in whom deafness was present and temporally related to the brain stem disorder bilateral symmetrical hearing loss was found

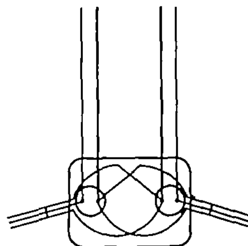


Fig 1 Schematic diagram of cochlear nerves and central pathways.

to be the rule. This is exemplified in Fig. 3 in which are shown the audiograms from 9 patients all with confirmed brain stem lesions including 3 cases of intramedullary glioma, 3 cases of cerebellar glioma involving the brain stem 2 cases of degenerative disease involving cerebellum and brain stem and 1 of diffuse vascular disease. The findings from autopsy operation or other investigations are summarised below:

B a woman of 25 was under the care Dr Gautier-Smith, and had had progressive deafness, ataxia of gait and clumsiness of arms for 15 years, together with intermittent regurgitation of fluids. Three paternal aunts and paternal grandmother were deaf since childhood. Posterior fossa decompression 11 years ago had demonstrated no abnormality but was followed by improvement.

Neurological examination revealed poor palatal movement and depressed gag reflex Tongue movements were slow and clumsy She had marked cerebellar ataxia, worse in left arm and leg with left hyper reflexia. Myelography showed a dilated fourth ventricle. A.E.G showed cerebellar atrophy

Neuro-otological abnormalities included a bilateral symmetrical perceptive deafness for all frequencies within the range 200–8 000 Hz; very severe for the higher tones. Loudness recruitment was complete as assessed by loudness discomfort levels. She had good toleration of amplified speech. Tone decay was present bilaterally at 1 000 2 000 and 4 000 Hz. First-degree spontaneous nystagmus of rebound type was present to left and right and upwards. Following movements and optokinetic responses were deranged, caloric responses exaggerated. There was positional nystagmus of central type.

Diagnosis: Familial degenerative process involving cerebellum and its vestibular and ocular connections including the cochlear pathways within the brain stem.

E. P., a woman of 50, was under the care of Dr Goody and complained of difficulty in focusing her eyes for 5 months with diplopia on lateral and downward gaze. She was unable to look up

Neurological examination revealed limited ocular elevation and convergence, impairment of tone, power and co-ordination of left arm A.E.G showed a mass in the region of the quadrigeminal plate producing obstruction of the upper third of the aqueduct.

Neuro-otological abnormalities included slight bilateral symmetrical deafness in the range 200–8 000 Hz. Loudness recruitment was complete as assessed by loudness discomfort levels. She had unsteadiness of gait. Convergence was absent and she was unable to look upwards and had first-degree vestibular nystagmus to right. Optokinetic responses showed directional preponderance to right and were present upwards but absent downwards. Caloric responses were exaggerated with directional preponderance to right.

Progress. Torkildsen's operation was performed with temporary relief of symptoms and she had a course of deep X-ray therapy. A year later she was admitted with recurrence of symptoms and ventriculography showed more severe hydrocephalus. She deteriorated and died. Autopsy was refused.

Diagnosis. Glioma in region of posterior

end of third ventricle involving the right vestibular and both cochlear pathways in the midbrain.

L. H., a woman of 45 was under the care of Mr McKissock, and had suffered for 4 years with severe frontal headaches and attacks of giddiness, nausea and vomiting. For 16 months she had difficulty in hearing and bilateral tinnitus unrelated to headache or vertigo.

Neurological examination revealed bilateral papilloedema with defective vision, worse in right than left eye. X rays of skull showed a crescent of linear calcification above and behind pineal region. Ventriculography demonstrated a tumour 3 cm diameter producing a filling defect of the third ventricle. Appearances suggested a globular tumour overlying the quadrigeminal plate with calcification of its posterior wall.

Neuro-otological abnormalities included a mild bilateral symmetrical perceptive deafness in the frequency range 200–4 000 Hz. She had some ataxia of gait deviating to right. Caloric responses showed slight directional preponderance to right.

Progress. Partial excision of an inoperable tumour was undertaken but patient died within 24 hours. Autopsy showed tumour arising from quadrigemina. Pathological report: Oligodendroglioma.

Diagnosis: Quadrigeminal plate glioma.

G. W., a man of 67 under the care of Professor Gilliatt. Eight years ago he had severe headache followed by unconsciousness after which he had vertigo and vomiting and mental confusion since when he has remained unsteady with mild deafness. Two years ago he became depressed. An A.E.G. 8 months ago showed communicating hydrocephalus but since this he developed urgency and incontinence of micturition and impaired memory.

Neurological examination revealed mild dementia, monotonous voice and expressionless face and mild ataxia of limbs. B.P. 220/115

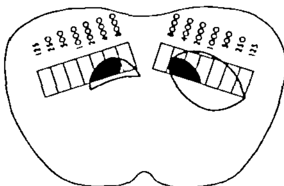


Fig. 2. Schematic diagram of left and right central cochlear pathways showing tonotopic arrangement of fibres. Shaded areas represent deafness resulting from asymmetric bilateral lesions.

Electrocardiography showed left ventricular hypertrophy. C.S.F. 100 mg Protein/ml. A.E.G. showed hydrocephalus with air over surface of hemispheres suggesting subarachnoid block.

Neuro-otological abnormalities included a progressively severe bilateral symmetrical perceptive deafness in the frequency range 200–8 000 Hz. Loudness recruitment complete as assessed by loudness discomfort levels. He had ataxia of stance and gait, falling or veering to right. Optokinetic nystagmus was deranged in character. Electro-nystagmographic records showed first-degree vestibular nystagmus to left and right abolished by eye closure and darkness.

Progress. A right V. A. Holter Rickham shunt operation was performed with resulting improvement in symptoms.

Diagnosis: Subarachnoid haemorrhage with resulting communicating hydrocephalus in a hypertensive patient following vascular accident involving the right vestibular and the cochlear neurones bilaterally at a high level in the brain stem.

J. M., a man of 59 was under the care of Dr Gooddy and complained of headache and feeling drunk for the past 10 days. He was unsteady on his feet and giddy on rising from a sitting posture.

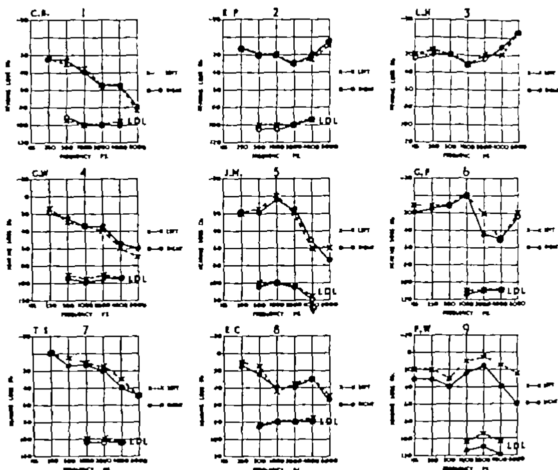


Fig 3 Audiograms of 9 patients with confirmed brain stem lesions: Cerebellar and Brain Stem Atrophy 1 and 8 Intramedullary Gliomata. 2, 3 and 9 Diffuse Vascular Disease: 4 Cerebellar Gliomata involving Brain Stem 5 6 and 7

Neurological examination revealed that he had severe nausea and vomiting on sitting up from a lying position.

Neuro-otological abnormalities included a symmetrical bilateral perceptive deafness in the frequency range 4 000–8 000 Hz. Loudness recruitment was present for the frequencies 500–2 000 Hz as assessed by loudness discomfort levels. He was very unsteady on standing, falling to right and was unable to walk. He had first-degree vestibular nystagmus to the left upward gaze was impaired. There was positional nystagmus of central type in the left lateral position. Caloric responses were exaggerated showing directional preponderance to left combined with right canal paresis.

Progress. Air encephalography revealed herniated cerebellar tonsils. At subsequent operation a cystic tumour was excised from right cerebellar hemisphere. The dura was under greatly increased tension. There was immediate post-operative improvement in the clinical condition but patient died 2 months later from B Pyocyaneus Meningitis.

Pathology Haemangioblastoma.

Diagnosis. Right cystic cerebellar glioma with secondary brain stem involvement implicating cerebello-vestibular cerebello-ocular and right vestibular pathways together with the intramedullary cochlear neurones bilaterally

G F a man of 59 was under the care of Mr McKissock and had 1 month s history

of occipital headache, difficulty with speech, giddiness and loss of power in right arm.

Neurological examination revealed cerebellar dysarthria with ataxia of right arm and leg. C.S.F. Protein 500 mg/100 ml.

Neuro-otological abnormalities included bilateral perceptive deafness substantially limited to the frequency range 2 000–8 000 Hz. Loudness recruitment present as assessed by loudness discomfort levels. He stood and walked very unsteadily falling to right. Slight first-degree vestibular nystagmus to left was present. He had positional nystagmus of central type and derangement of optokinetic nystagmus which was worse to right than left. The left caloric responses were reduced.

Progress. A right cystic cerebellar tumour was excised which extended into the fourth ventricle. Good recovery.

Pathology: Haemangioblastoma.

Diagnosis. Right cerebellar glioma involving cerebello-vestibular vestibular and cochlear pathways bilaterally within the brain stem.

T. S., a man of 58, was under the care of Dr Ross Russell, and had throbbing morning headaches for 14 months in the right temporo-occipital region, aggravated by coughing, laughing or straining. He also had progressive weakness and unsteadiness of legs, deviating to right on walking. He had noticed right-sided deafness in past 6 months.

Neurological examination revealed spastic quadriparesis, worse in legs, with bilateral cerebellar signs worse right than left. Ventriculography showed dilatation of lateral and third ventricles with displacement to left of fourth ventricle.

Neuro-otological abnormalities included a p[illegible]ssively severe bilateral perceptive deafness in the range 200–8 000 Hz. Loudness recruitment was complete as assessed by loudness discomfort levels. He was more easily pushed to right than left on standing and deviated to right on walking with eyes closed. Upward gaze and convergence were limited and optokinetic responses sluggish. Electronystagmographic records showed much saccadic movement in darkness. Caloric responses showed directional preponderance to left.

Progress. Vascular tumour lying posterolaterally in right cerebellar hemisphere and fed by posterior inferior cerebellar artery was removed with good recovery including improved eye movements.

Pathology: Haemangioblastoma.

Diagnosis. Right cerebellar glioma displacing brain stem and involving cerebello-ocular right vestibular and intramedullary cochlear pathways bilaterally.

E. C., a woman of 67, was under the care of Dr Gooddy and had had four brief episodes of dizziness 9 months ago. For the past 4 months she had progressive unsteadiness of gait with clumsiness of hands.

Neurological examination revealed trunkal ataxia with cerebellar inco-ordination of all four limbs particularly legs and very brisk deep tendon reflexes. The right plantar response was extensor.

Neuro-otological abnormalities included bilateral symmetrical perceptive deafness in the frequency range 200–8 000 Hz, more severe for the higher tones. Loudness recruitment was complete as assessed by loudness discomfort levels. She had ataxia of gait and directional preponderance to left of caloric responses.

Progress: Balance deteriorated steadily. She developed positional nystagmus of central type and died 2 years later. Autopsy showed generalised cerebellar atrophy with a pons diminished in size. Microscopically cells of pontine nuclei were diminished in numbers with fibrous gliosis, axons thin with faintly staining myelin sheaths.

Diagnosis. Olivo-ponto-cerebellar atrophy involving cerebello-vestibular and central cochlear pathways bilaterally.

F. W., a woman of 48, was under the care of Mr McKissock, and had had intermittent

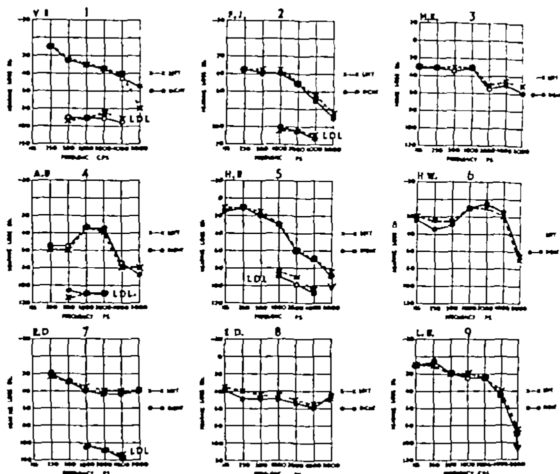


Fig. 4 Audiograms of 9 patients with brain stem lesions diagnosed on clinical findings: Multiple Sclerosis. 1 Vascular Disease 2, 3 4 5 7 and 9. Intra-medullary Metastases: 6. Pellagra. 8.

discharge from right ear for years. Two months ago she had developed diplopia, headaches, numbness of left side of face with loss of taste ataxia and stiffness of limbs, particularly on right side.

Neurological examination revealed dysarthria, diplopia in all directions of gaze, with left trigeminal loss both motor and sensory She had right lower motor neurone facial weakness and weakness of left side of palate and all four limbs with pyramidal signs and inco-ordination with marked weakness and impaired superficial sensation on right side. Ventriculography demonstrated dilated lateral and third ventricles with posterior displacement of fourth ventricle suggesting a pontine tumour A limited A.E.G demonstrated pontine enlargement. Vertebral arteriography confirmed a space-occupying lesion in the pons more on left side with upward tentorial herniation.

Neuro-otological abnormalities included a slight bilateral symmetrical perceptive deafness. This was complicated on the right side by a superimposed conductive deafness due to an active right chronic suppurative otitis media. Loudness recruitment was complete bilaterally as assessed by loudness discomfort levels, the loudness discomfort level in the right being elevated only by the amount of the conductive deafness. There was an abductor paresis of the left vocal cord. Spontaneous nystagmus was present to left and right and upwards with positional nystagmus of central type and absent optokinetic responses to right and downwards. Caloric responses were

grossly exaggerated with directional preponderance to left.

Diagnosis. Intramedullary glioma involving right vestibular neurones and left nucleus ambiguous, the cerebello-vestibular and central cochlear pathways being involved bilaterally within the brain stem.

With the exception of Case F W in which the difference in hearing levels at the two ears could be attributed to a conductive defect the bone conduction audiograms confirmed the hearing loss in the remainder to be sensorineural in origin. The symmetricality of the hearing loss at the two ears is self-evident. In addition it will be seen that the Loudness Discomfort Levels are within the normal range and therefore indicate the presence of complete recruitment. This is a finding of some significance and we shall return to it later

In Fig. 4 are shown the audiograms of a selection of patients with brain stem lesions unconfirmed by operation. Summaries of the clinical findings in each are as follows.

V E. a woman of 60 was under the care of Professor Gilliatt, and had had progressive difficulty in walking for 15 years, urgency of micturition, stress incontinence, blurred vision, diplopia and, more recently parasthesiae involving fingers of right hand and feet.

Neurological examination revealed bilateral intention tremor and exaggeration of reflexes in upper limbs, weakness of lower limbs with ankle clonus and hyper-reflexia. Vibration sense was absent in right leg.

Neuro-otological abnormalities included severe ataxia of stance and gait, spontaneous nystagmus to left and right of rebound type, inhibited in darkness and abolished by eye closure. Following movements were broken up and optokinetic responses sluggish. Caloric responses showed directional preponderance to left combined with right canal paresis.

Diagnosis. Multiple Sclerosis with cerebellar and pyramidal involvement and lesions of right vestibular and both cochlear pathways within the brain stem.

F J., a man aged 66 was under the care of Professor Gilliatt, and, 3 months ago had sudden loss of consciousness with paralysis of legs, vertigo and vomiting and had been temporarily deaf The legs gradually recovered. He had throbbing, occipital headache 20 years ago

Neurological examination of fundi revealed arteriolar narrowing. He had a right temporal hemianopia and constriction of left temporal field. There was bilateral heel/shin ataxia.

Neuro-otological abnormalities included bilateral symmetrical perceptive deafness, more severe for the higher tones, associated with loudness recruitment as assessed by the loudness discomfort levels. He had ataxia of gait, reduction of left caloric responses and inconsistent deviations in both directions of assessment of the visual vertical and horizontal.

Diagnosis: Vascular insufficiency with cerebellar and posterior cerebral lesions and recent vascular accident involving the central cochlear pathways and left vestibular neurones within the brain stem.

M. K. was a woman of 69 under the care of Dr Critchley She had deteriorated mentally and physically over the past year and suffered from falling attacks without vertigo or loss of consciousness, for 6 months.

Neurological examination revealed mild dysphasia and slurring dysarthria. All tendon reflexes were exaggerated and plantar responses extensor

Neuro-otological abnormalities included bilateral perceptive deafness and ataxia of stance and gait. There was defective upward gaze and 1st vestibular nystagmus to left and right. Optokinetic responses were defective in the vertical plane. Caloric responses showed slight reduction of the left reactions.

Diagnosis. Diffuse cerebro-vascular disease affecting cortex, anterior mid brain pathways

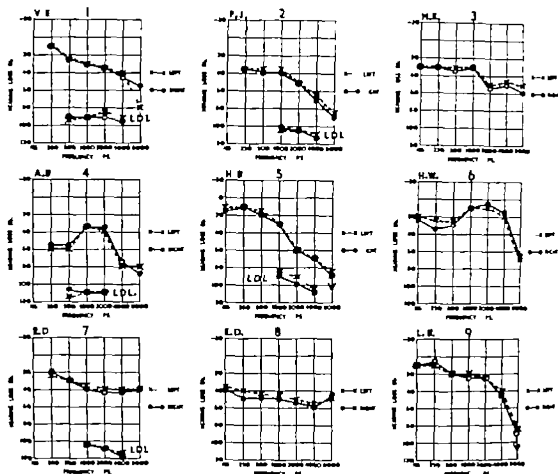


Fig. 4 Audiograms of 9 patients with brain stem lesions diagnosed on clinical findings: Multiple Sclerosis: 1 Vascular Disease 2, 3, 4 5 7 and 9. Intramedullary Metastases 6. Pellagra. 8.

discharge from right ear for years. Two months ago she had developed diplopia, head aches, numbness of left side of face with loss of taste, ataxia and stiffness of limbs, particularly on right side.

Neurological examination revealed dysarthria, diplopia in all directions of gaze, with left trigeminal loss both motor and sensory She had right lower motor neurone facial weakness and weakness of left side of palate and all four limbs with pyramidal signs and inco-ordination with marked weakness and impaired superficial sensation on right side. Ventriculography demonstrated dilated lateral and third ventricles with posterior displacement of fourth ventricle suggesting a pontine tumour A limited A.E.G demonstrated pontine enlargement. Vertebral arteriography confirmed a space-occupying lesion in the pons more on left side with upward tentorial herniation.

Neuro-otological abnormalities included a slight bilateral symmetrical perceptive deafness. This was complicated on the right side by a superimposed conductive deafness due to an active right chronic suppurative otitis media. Loudness recruitment was complete bilaterally as assessed by loudness discomfort levels, the loudness discomfort level in the right being elevated only by the amount of the conductive deafness. There was an abductor paresis of the left vocal cord. Spontaneous nystagmus was present to left and right and upwards with positional nystagmus of central type and absent optokinetic responses to right and downwards. Caloric responses were

weeks ago this had been associated with vertigo, vomiting and weakness and cramp in the legs. She had a feeling of being tilted to the left and had diplopia, slurred speech, headache and weakness and clumsiness of left hand. All symptoms were improving.

Neurological examination revealed impaired sensation to pain and temperature over right cheek, right side of trunk and right lower limb together with weakness and incoordination of left leg. B.P 220/75 There was evidence of coronary infarction.

Neuro-otological abnormalities included a bilateral symmetrical perceptive deafness with loudness recruitment present as assessed by loudness discomfort levels. She was ataxic on standing and walking. The caloric responses were a little exaggerated with relative reduction of the left reactions.

Diagnosis. Hypertension with recent brain stem vascular accident.

E D., a woman of 43 was under the care of Professor Dent, and gave an 8 year history of episodes of lassitude, depression, deafness and weight loss in which her skin had become dry dark and thick. She had diarrhoea and the difficulty in hearing was worse at times of attacks. Marked improvement in symptoms on each occasion had resulted from Nicotinic Acid therapy

Neurological examination revealed dark pigmentation of skin with hyperkeratosis of ankles and dorsum of hands. She was mentally confused and disorientated with spastic quadriparesis and extensor plantar responses, ankle and patellar clonus.

Neuro-otological abnormalities included bilateral symmetrical perceptive deafness. The caloric responses were exaggerated bilaterally with normal pattern. There was patchy pigmentation of palate.

Diagnosis Pellagra involving intramedullary cerebello-vestibular and cochlear pathways bilaterally

L. B., a woman of 64 was under the care of Dr Williams, and had had difficulty in walking during the past year Her hearing had been deteriorating some 4-5 years.

Neurological examination revealed multiple neurofibromata of skin with exaggerated tendon reflexes and extensor plantar responses. She had complete achlorhydria. B.P 240/120 E.E.G showed episodic activity considered to be a result of brain stem ischaemia.

Neuro-otological abnormalities included bilateral symmetrical perceptive deafness in the range 500-8 000 Hz, severe at 8 000 Hz. She had ataxia of stance and was unable to walk with the eyes closed. There was positional nystagmus of central type and exaggeration of caloric responses with normal pattern.

Diagnosis. Diffuse organic defect involving the cerebello-vestibular pathways and cochlear neurones bilaterally within the brain stem likely to be due to vascular insufficiency associated with her hypertension.

Once again a feature of all the above cases is the symmetricality of the hearing loss at the two ears and in addition, according to the loudness discomfort levels, loudness recruitment seems to be the rule.

DISCUSSION

It can be argued that the hypothesis we have presented to account for this symmetricality is unnecessary since our findings might equally well be explained in terms of symmetry of the lesion of the kind commonly encountered in congenital hearing loss. Deafness due to kernicterus is a case in point.

The audiograms of six typical cases are shown in Fig. 5 In these the lesion is known to involve the cochlear nuclei themselves (Bertrand, 1946 Crabtree & Gerrard, 1950; Dublin, 1951 Gerrard, 1952) and on this account in accordance with our hypothesis it must be presumed that the symmetry of the hearing loss reflects a similar symmetry of the lesion. While it cannot be denied that this explanation needs to be taken into account

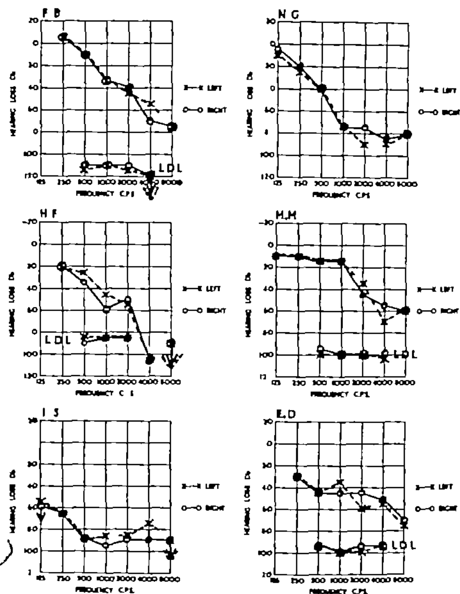


Fig. 5. Audiograms of 6 patients with deafness due to Kernicterus.

considering the cases in our series the probability of such a wide variety of brain stem lesions giving rise to symmetrical bilateral degeneration of the cochlear nuclei would seem to be a remote one.

A second possibility that neeeds to be considered is that the deafness resulted from either a symmetrical bilateral nerve fibre or cochlear lesion. The former can certainly be ruled out since it will be recalled that loudness recruitment was a constant finding in all of our cases. As to the latter in all the cases reported here it will be recalled that the deafness was shown to be a related symptom of the disorder The occurrence of a coincidental cochlear lesion therefore would imply a statistical improbability Nevertheless the consistent finding in our cases of loudness recruitment, a phenomenon which has long been taken to be characteristic of and restricted to cochlear lesions, remains to be explained. More recent studies including those of Liden (1969) and Carhart (1967) incline to the view that loudness recruitment is a feature of brain stem disorders. In this respect the occurrence of recruitment in all of the cases of kern

icterus reported here in which the test was carried out is of some significance. Blakeley (1959), Flottorp et al. (1957) and Matkin (1965) have all reported similar findings. In addition there is now a substantial body of histopathological evidence based upon the examination of temporal bones (Wolf 1956 Crabtree & Gerrard, 1950 Gerrard, 1952, Goodhill, 1956) that end organ involvement is conspicuously absent in kernicterus. In this respect it is of some significance that in all the cases we have examined the caloric responses have been normal. This would suggest that the lesion is at a level where the cochlear and vestibular fibres have separated It must be inferred therefore that the presence of recruitment in these cases results from derangements of the cochlear nuclei.

This occurrence of loudness recruitment in brain stem lesions has obvious and important theoretical implications outside the scope of this discussion. Suffice it to say here that it would seem to imply either that the mechanism of recruitment in brain stem lesions differs from that commonly attributed to end organ lesions or else some revision of the latter is called for

Our studies are continuing and we hope in due course to be able to support our hypothesis with histopathological evidence. In this event the recognition of symmetrical hearing loss exhibiting loudness recruitment in patients with known or suspected brain stem lesions could well be a localising sign of some significance.

The cases referred to in this paper included the following Hospital Numbers (N.H.Q.S.): A65504 A9455 A36450, A43008, 53465 52163 A61507 A10241 A40289 A26277 A16195 A10901 A47037 A9327 A25473 78050, A22855 A22243 A40395 81906, A51643 A52715 A24393

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RÉSUMÉ

L'examen de patients souffrant d'atteintes confirmées du tronc cérébral, avec hypoacousie bilaterale a montré que l'atteinte auditive tonale est pratiquement toujours identique pour les deux oreilles. Cette constatation a des implications *théoriques intéressantes* en ce qui concerne l'organisation somatotopique des voies auditives dans le tronc cérébral. Elles seront le sujet d'une discussion.

ZUSAMMENFASSUNG

Untersuchungen von Fällen von bilateralem Gehörmangel durch erwiesene Mittelhirnherden verursacht, haben gezeigt, dass die Reinton-Audiogrammen der zwei Ohren stets identisch sind. Dieser Befund hat interessante theoretische Konsequenzen über die tonotopische Organisation der Gehörverbindungen im Mittelhirn: diese werden weiter besprochen.

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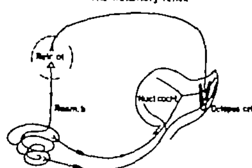
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DISCUSSION

P Pialoux. J'ai été très intéressé, car j'ai observé moi-même plusieurs malades atteints de lésions du tronc cérébral, du point de vue auditif J'ai constaté l'atteinte symétrique. Cependant je voudrais me permettre quelques réserves l'étiologie paraît jouer un rôle dans cet aspect séméiologique Par exemple si ce dernier se retrouve de façon presque constante dans les tumeurs du IVe ventricle il paraît exceptionnel dans les gliomes du tronc cérébral. Cette constatation amène à penser que l'un des éléments jouant un role dans l'atteinte auditive symétrique pourvait être la situation anatomique de la lésion médiane au niveau des noyaux cochléaires ou de la crusation.

R. Hinchcliffe I would congratulate Miss Dix on tackling a problem which in its more general aspect has puzzled audiologists for many years, i.e. the frequent symmetricity of tonal threshold audiograms. This applies not only to the types of lesions which she has studied but also to lesions of the internal and middle ear Of course there is also the possibility of double coincidental lesions of which, I am sure, she is aware.

G Liden I want to compliment Miss Dix for her very interesting paper Poole and Hood stated recently that an increased level of loudness discomfort (LDL) was a good indicator of retrocochlear deafness. The cases of Miss Dix seemed to have a normal LDL. Were any supplementary audiological tests done to exclude the possibility of simultaneous lesion in the cochlea?

C R. Pfaltz Lesions of the cochlear nuclei are causing integrational disturbances of the process of hearing. I should like to ask Miss Dix if she has carried out any integrational hearing tests such as Bocca's or Feldmann's test to find further evidence for the presence of a central, i.e. integrational, deafness in the group of patients

J M Aran. Very shortly I hope to report some observations we have made on the VIII nerve responses in one case of brain stem degeneration, in kernicterus cases and also in retrocochlear lesions. These observations could help in the discussion of Miss Dix' presentation and support her hypothesis, particularly about the possibility of a central origin for loudness recruitment in some instances. In the case of brain stem degeneration we recorded absolutely normal responses showing no recruiting phenomenon. In the kernicterus cases as well as in most of the retrocochlear disorders we always observe very abnormal distorted patterns which indicate that the lesion must be also partly peripheral. *Also in the kernicterus cases* the recordings are quite similar symmetric, on both sides.

J G Hall. As to kernicterus, you will see in my thesis from 1964 that there is a great loss of nerve cells in the cochlear nuclei following kernicterus. The bilirubin hampers the oxygen carrying ability of the haemoglobin so the cells disintegrate, either from the toxic effect of the bilirubin or of asphyxia

As to the possibility of a central recruitment, a paper was presented on this topic by Lidén, Engström and myself in Gothenburg, this year Due to new neuroanatomical findings, the nervous pathways producing a "central recruitment" may be described. Dr Kirsten Osen described the octopus cells in the dorsal part of the dorsoventral cochlear nucleus. These cells are so situated that incoming impulses must pass through their area. Their afferents pass to the retro-olivary bundle where the efferent bundle of Rasmussen originates, carrying inhibitive impulses (Fig 1). This short reflex consisting of three neurones has a constant tonus, inhibiting unwanted impulses. Now if this tonus should be disturbed, due to a disease or due to a tumour somewhere along its course the inhibition would fail, the impulses pass undisturbed, and you would have a "central recruitment"

M Dix (Reply) to Mr *Pialoux* Dr Dix said that bilateral symmetrical deafness had certainly been encountered in patients with proven neurological abnormalities rostral to the level of the cochlear nuclei as for example in cases E. P and L. H. with phenom

involving the quadrigeminal plate and G W with communicating hydrocephalus and electronystagmographic evidence of a high brain stem lesion. Although there was no clinical evidence that these lesions extended distally to involve the IV ventricle or cochlear nuclei this possibility could not of course be excluded.

Mr *Hinchcliffe*: Dr Dix pointed out that examinations of the ears and tests of bone conduction had been entirely normal apart from the single case of F W. This finding taken together with the fact that the complaint of or demonstration of symmetrical deafness had been related to central disorders of such a wide variety would make the likelihood of a coincidental cochlear lesion a statistical improbability. This view was fortified by the demonstration of bilateral symmetrical deafness in kernicterus, a condition in which the lesion was known to involve the brain stem and in which normal cochleas had been demonstrated histologically.

Mr *Lidén*. Dr Dix pointed out that what had been stated by Hood and Poole (1966) was that with an elevated or absent Loudness Discomfort Level "the lesion has an extremely high probability of the order of 9 cases out of 10 of being in the nerve fibre". No reference was made to the findings in brain stem lesions. Tone decay tests carried out more recently on a number of patients with brain stem lesions had demonstrated abnormal results in a significant proportion whereas with cochlear lesions the presence of tone decay was exceptional. (Morales-Garcia and Hood, 1972.) As an example, in the case of C.B. in the present study tone decay was present at all frequencies tested, this amounted to 35 decibels at 4 000 Hz.

Mr *Pfaltz*: Dr Dix said that although no tests of integrational deafness had been carried out on the group of patients in the present study further work on a group of 15 patients with brain stem lesions had shown that their masked speech scores were significantly lower than those of normal subjects but no correlation had yet been established with respect to the level or lateralisation of the lesion (Morales-Garcia and Poole, 1972).

Mr *Hall*. Dr Dix thanked him for his kind and helpful remarks. The neuro-anatomical mechanisms which he described would purport to be most appropriate and would provide just such an explanation as we had been looking for to account for central recruitment.

Acta Otolaryng 75 178–183 1973

A COMPARISON BETWEEN MIDDLE EAR MUSCLE REFLEX THRESHOLDS FOR BONE AND AIR-CONDUCTED PURE TONES

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Abstract. The middle-ear muscle reflex threshold for bone-conducted pure tones (250–6 000 Hz) was compared with the corresponding threshold for air-conducted tones. In normal-hearing subjects a significant difference (5–25 dB) was found. Possible causes for this discrepancy were studied.

It is well known that acoustic stimulation of high intensity produces bilateral changes in the acoustic impedance of the ear These impedance changes are brought about by reflex contractions of the middle-ear muscles. The middle-ear muscle reflex threshold for air conducted pure tones is 70–90 dB sensation level (Jepsen 1955) This has been confirmed by numerous investigators.

The corresponding reflex threshold for bone-conducted pure tones has, until now only been studied in a few patients with Menière's syndrome in which the findings were difficult to evaluate (Djupesland, 1964)

The main purpose of the present investigation was to determine the middle-ear muscle reflex threshold (from now on referred to as "the reflex threshold") for bone-conducted pure tones in normal-hearing subjects and to compare it with the threshold for air-conducted tones.

MATERIAL AND METHOD

Our material consisted of 7 subjects with normal hearing in both ears (3 female, aged 19–26 years, and 4 male, aged 27–46 years) and 7 subjects with normal hearing in one ear the contralateral being totally deaf (2 female, aged 23–59 years, and 5 male, aged 16–35 years). In all subjects the contralateral ear and the tympanic membrane had a normal appearance.

The reflex contractions of the middle-ear muscles were studied by means of a Madsen Electro-Acoustic Impedance Bridge (Model ZO 70). Using bridge sensitivity setting 3, the reflex threshold was defined as the stimulus intensity giving approximately 10% of maximal obtainable impedance change.

The middle-ear pressure was measured as described by Terkildsen & Thomsen (1959) and found to be normal in all cases. In all ears, even in the totally deaf ones, changes in the acoustic impedance of the ear could be elicited by touching the skin around the opening of the ipsilateral and the contralateral auditory meatus with cotton wool (tactile stimulation). These findings indicate normal middle-ear function (Djupesland, 1967 1969).

The subject was positioned on an examination table in a soundproof and almost anechoic chamber The head was placed on a cushion so that the mastoid process was in a horizontal position. Through an opening in the cushion, the ear was connected to the impedance bridge (Fig. 1) In the unilaterally deaf subjects, the impedance bridge was always connected to the deaf ear

The signals, giving air and bone-conducted pure tones, were delivered from a Peters



Fig. 1. Subject placed on the examination table with Mini Shaker (→) applied to the right mastoid process and the left ear connected (⇄) to the impedance bridge.

Audiometer type SPD 5. The duration of each signal was approximately 1.5 sec. The signals were either directly delivered to a earphone (Telephonics TDH 39) or amplified and delivered to a Mini Shaker (Bruel & Kjær Type 4810) or a loudspeaker (Tandberg BK 165). A block diagram of the equipment is shown in Fig. 2. The audiometer was calibrated according to the ISO 1964 standard. The harmonic distortion and the maximum output of the Mini Shaker were determined. Results are shown in Table I.

The sound-pressure level generated by the loudspeaker was measured at the ear of the subjects with a Brüel & Kjær Precision Sound Level Meter Type 2203 equipped with an octave filter set, Type 1613.

The Mini Shaker was placed on the mastoid process facing upwards, without contact with the pinna (Fig. 1). The pinna was bent somewhat in a forward direction, using adhesive tape. (The ear canal was not occluded.)

Hearing threshold and reflex measurements

Using the earphone and the Mini Shaker the hearing thresholds for the frequencies 250, 500, 1 000, 2 000, 3 000, 4 000 and 6 000 Hz were measured by the method of limits. In addition the reflex thresholds for air and bone-conducted pure tones were determined for the same frequencies. All measurements were performed at three different times for the normal hearing subjects, and in one session only for the unilaterally deaf persons.

Loudness balance test

Since the middle ear muscle reflex in man is loudness governed (Metz, 1952, Ross 1968, Flottorp et al. 1971 and others), we thought it of interest to perform loudness balance test between air and bone-conducted sounds according to the method of Fowler (1936).

In the normal-hearing subjects the impedance bridge was disconnected, keeping the rubber plug and the two polyethylene tubes in the ear canal. The polyethylene tubes were connected to a TDH 39 earphone, using an adapter.

In the unilaterally deaf subjects, the loudness balance test refers only to one ear. The earphone and the Mini Shaker could not be placed simultaneously on the same side. Therefore, the earphone was replaced by a loudspeaker hanging 35 cm above the entrance of the ear canal. The hearing threshold measurements, both for air and bone-conducted sounds, were repeated in order to relate all loudness levels to threshold values.

Control experiments

To make sure that the observed impedance changes were caused by middle-ear muscle contractions and not by artefacts (for in-

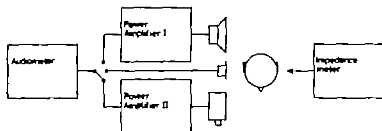


Fig. 2. Block diagram of the equipment showing the 3 different types of sound sources: loudspeaker, earphone and Mini Shaker stimulating one ear. Impedance meter connected to the opposite ear.

stance, interference between the stimulus tone and the probe tone of the impedance bridge) some supplementary experiments were carried out. Three totally deaf persons with normal tympanic membranes and 3 with tympanosclerosis on one side and normal hearing on the other side served this purpose. In the deaf subjects, ear canal irrigations with water at temperatures of 44, 30 and 4 degrees Centigrade respectively were not followed by nystagmus, indicating that the labyrinths were out of function. However, tactile stimulation elicited reflex contractions of the middle-ear muscles on both sides, indicating normal middle-ear function.

Using air- and bone-conducted pure tones of maximal obtainable intensity (Table I) no impedance changes were observed in any of these subjects. These findings indicate that the acoustically elicited impedance changes, observed in the present investigation were caused by genuine reflex contractions of the middle-ear muscles and not by artefacts.

RESULTS

The reflex thresholds for air- and bone-conducted pure tones in normal-hearing persons are presented in Figs. 3 and 4. In Fig. 3 the hearing as well as the reflex thresholds are presented relative to normal hearing thresholds for air (ISO 1964) and bone-conducted pure tones (DAI 1972).

The values in Fig. 4 are related to the hearing thresholds measured individually just before the determination of the reflex thresholds.

As shown in Figs. 3 and 4 a considerable difference between reflex thresholds for air- and bone-conducted pure tones was found, especially in the low frequency range. This difference amounted to 5–25 dB.

In the high frequency range, middle-ear muscle reflex could not be elicited in all subjects for bone-conducted stimuli, even when maximum intensity (Table 1) was used (circled symbols 2 000–6 000 Hz).

At high intensity levels of the frequencies 250, 500 and 1 000 Hz, the Mini Shaker in all cases produced a tingling sensation localized in the area below the bone vibrator. A distinct threshold for the tingling sensation was found except for the high frequency range (2 000–6 000 Hz) where no such sensation was reported. The threshold of the tingling sensation coincided with the reflex threshold.

The results of the loudness balance tests are plotted in Fig. 4. The rate of loudness increase as a function of sensation level was approximately the same for air- and bone-conducted pure tones.

The results for the unilaterally deaf subjects were practically identical with those reported for the normal-hearing group.

DISCUSSION

The results have shown that in normal-hearing subjects there is a considerable difference in reflex thresholds for air- and bone-conducted pure tones. The middle-ear muscle reflex in man, elicited by *air-conducted* pure tones, seems to be loudness governed (Metz, 1952, Ewertsen et al., 1958, Djupesland & Flottorp, 1970, Flottorp et al., 1971). Therefore, the observed difference indicates that

Table I. *Harmonic distortion and maximum level of Mini Shaker*

Frequency (Hz)	Level of harmonic components in dB re 1 mV			Max. output in dB re bone conduction threshold (DAI)
	1 H	2 H	3 H	
250	50	28	2	68
500	49	27	1	73
1 000	41	−12	−34	81
2 000	26	−38	−34	75
3 000	17	−40	−35	65
4 000	12	−30	−12	65
6 000	11	−35		70

The reference zero for bone-conduction (DAI) in the Table is based upon an investigation carried out at our institute (Det Audiologiske Institutt, DAI) not yet published, however proposed as a preliminary "standard" until such has been established by ISO

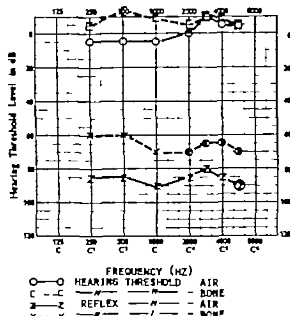


Fig. 3. Hearing and "reflex" threshold for air and bone-conducted tones in normal-hearing persons.

the reflex mechanism for bone-conducted pure tones cannot be loudness governed. This is further supported by the results of the loudness balance experiments, which show approximately the same rate of loudness increase for air and bone-conducted pure tones.

Among the pronounced differences between the two types of stimuli the following may be mentioned.

(*a*) The bone vibrator (*Mini Shaker*) was in direct contact with the skin, thereby adding the possibility of tactile stimulation of the reflex mechanism (Djupesland, 1967) whereas the air-conducted tones do not produce any tactile sensation.

(*b*) The Mini Shaker stimulates both cochleae with almost the same intensity whereas the air-conducted tones only affect one ear

In order to investigate whether the difference in reflex eliciting mechanisms might be due to one or both of the above-mentioned modes of stimulation, experiments were conducted, excluding the tactile possibility by means of anaesthesia, and binaural summation by using unilaterally deaf subjects.

(*a*) The skin between the Mini Shaker and the mastoid process was anaesthetized by injections of 5 ml of Xylocain® 1% in 3 subjects. The reflex threshold was found to be the same as before the injection. Therefore, the possibility of a tactile-elicited reflex can be excluded. Further support for this exclusion is the fact that in the previously mentioned totally deaf subjects, maximum stimulation with the Mini Shaker caused no impedance change.

(*b*) Seven subjects with normal hearing in one ear and a deaf contralateral ear showed no significant difference in reflex thresholds from the seven normal-hearing subjects. Thus a possible binaural summation effect can be excluded.

The subjects reported that the tonal sensation changed at and above the tingling sensation threshold. We therefore initiated an investigation of the content of aural harmonics in normal-hearing subjects for bone-conducted pure tones. The method of "best beats" was used (Opheim & Flottorp, 1955).

Our results so far seem to indicate that unusual overload of the inner ear starts at the tingling sensation threshold. Therefore, a possible difference in inner ear distortion

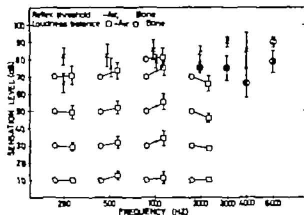


Fig 4 "Reflex threshold and equal lodness for air and bone-conducted tones in normal-hearing persons.

for air and bone-conducted pure tones may be responsible for the difference in reflex thresholds.

RÉSUMÉ

Le seuil d'exitation du reflexe musculaire de l'oreille moyenne sollicité par des sons purs (250–6 000 Hz) conduits par voie osseuse est comparé avec le seuil correspondant pour des sons conduits par l air Chez des sujets à audition normale, on a trouvé une dif férence significative (5–25 dB). Les causes possibles de cette différence ont été recherchés.

ZUSAMMENFASSUNG

Die Mittelohrmuskelreflexschwelle bei knochengeleiteten, reinen Tonen (250–6 000 Hz) wurde verglichen mit der entsprechenden Schwelle bei luftgeleiteten Tönen. Bei Normalhorigen wurde ein signifikanter Unterschied (5–25 dB) festgestellt. Mogliche Ursachen dieses Unterschieds wurden studiert

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Norway

DISCUSSION

G Lidén. I agree that it is a great advantage to be able to elicit the stapedial reflex at about 30 dB lower level than with a conventional technique. However bone vibrators of commercially available audiometers do not seem to be able to do so. I wonder if Mr Djupesland has excluded the possibility of physical interference between the stimulus and the carrier tones?

R. Hinchcliffe Mr Djupesland has mentioned most of the possible sources of error but I wonder whether he could comment on the possibility that there is acoustic interference with the operation of the impedance bridge. As he knows, one of the modes of bone transmission is via the air in the external acoustic meatus—and this would also be on the air fitted with the impedance bridge

G Djupesland (Reply) to Mr *Lidén*: An ordinary bone vibrator cannot be used to measure the middle ear muscle reflex threshold in normal-hearing persons because of limited output and non-linearity at high intensity levels.

To Mr *Hinchcliffe* The problem concerning recording artefacts for example interference between the stimulus tone and the probe tone (carrier tone

of the impedance bridge) was studied using 3 totally deaf persons with normal tympanic membranes and 3 patients with tympanosclerosis on one side and normal hearing on the other side. In the present paper these control experiments are reported (not mentioned during my presentation) The results indicated that the acoustically elicited impedance changes, observed in the present investigation, were caused by genuine reflex contractions of the middle-ear muscles and not by artefacts.

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THE EFFECTS OF ETHACRYNIC ACID UPON THE COCHLEAR ENDOLYMPH AND STRIA VASCULARIS

A Preliminary Report

S. K. Bosher C. Smith and R. L. Warren

From the Ferens Institute of Otolaryngology Middlesex Hospital Medical School University of London London England

Abstract. The normal endocochlear potential was rapidly replaced by a negative anoxic-type potential after ethacrynic acid administration (60 mg/kg) in the rat Recovery at first proceeded quickly but became very much slower at 30 min. However the endolymphatic chemical composition remained unaltered until 35 min when progressive increase in the sodium and decrease in the potassium concentrations occurred, followed at 1 hour by a gradual return towards normal. Thus the drug probably causes transient inhibition of the strial enzymes and then abnormalities in membrane permeability The characteristic accumulation of inter-cellular fluid in the stria vascularis was associated with and seemed to arise from these permeability changes. In addition, the findings strongly port the concept that the endocochlear potential two components, a positive secretion potential nd a negative potassium diffusion potential.

The discovery early in its clinical use, that both transient and permanent deafness could be produced by the diuretic agent, ethacrynic acid, has been followed by a number of investigations into the possible mechanism of its action upon the cochlea. Of particular prominence in the initial period were those studies showing the cochlear microphonic responses to be depressed and often abolished by the drug under a wide variety of conditions (Mathog et al. 1970). In addition, electron microscopic examination has considerably increased our knowledge of the effects induced for not only has the occurrence of the degeneration of the basal outer hair cells described first in human material (Matz et al., 1969) been confirmed, but the presence of morphological abnormalities in the stria vascularis has also been revealed (Quick & Duvall, 1970).

This discovery of strial involvement led naturally to the suggestion that alterations in endolymph composition might have an important role in the pathogenesis of the deafness and, latterly direct experimental evidence about such a possibility has been obtained (Cohn et al. 1971 Silverstein & Yules 1971) The rather diverse results, however are difficult to interpret and nothing is known about possible disorders of the endolymphatic anion content. Furthermore, no information was available concerning the endocochlear potential, a vital factor in determining the ionic gradients, until the recent report by Prazma and his colleagues (1972) These authors were, in fact, able to demonstrate the presence of marked variations in this potential and to correlate these variations with the effects observed upon the other cochlear potentials, but they did not themselves investigate the ionic concentrations of the inner ear fluids in their animals.

The present investigation was therefore undertaken to determine the extent of the changes in the endocochlear potential and the endolymphatic constitution following ethacrynic acid administration in a single species and

to correlate these, as far as possible, with the ultrastructural anomalies produced in the stria vascularis, in order to determine the nature of the drug's deleterious action upon the endolymph system.

MATERIAL AND METHODS

Adult white Wistar rats, body weight 200 g, were used for the experiments and anaesthetized with Urethane (1 66 mg/kg body weight by intra-peritoneal injection) Ethacrynic acid, as sodium ethacrynate (12.5 mg/ml solution), was administered by intravenous injection into the left femoral vein in a dose of 60 mg/kg body weight, the injection time being 25–30 seconds.

The acoustic stimuli for the cochlear microphonic responses, 2kH, tone pulses of 100 ms duration, were produced by means of a Brüel & Kjær type 1024 sine random generator and delivered through a Brüel & Kjær type 4216 constant sound pressure source placed 6 inches from the animal's intact left external ear The stimulus level was adjusted to give a signal magnitude of 90 dB (re 2×10^{-5} N/m^2), as recorded by a half-inch condenser microphone placed in the position of the animal's tympanic membrane and measured by a Brüel & Kjær type 2606 measuring amplifier The cochlear microphonic potentials were recorded using a stainless steel wire electrode placed on the bony margin of the round window after the left bulla had been opened in the post-auricular region. The potentials were amplified by means of a Tektronix 3A9 unit, displayed on a Tektronix 565 oscilloscope and photographed with a Tektronix C27 camera.

Details of the experimental procedures for the measurement of the endocochlear potential and the collection of samples of the inner ear fluids, together with the analytical methods employed will be found in two previous publications (Bosher & Warren, 1968, 1971) to which reference should be made

Animals selected for ultrastructural examination were sacrificed by decapitation 2 hours post-injection, after the removal of endolymph from the left cochlea. The temporal bones were removed and the cochleae fixed for 2 hours by either phosphate-buffered (pH 7.2–7 4) 1% osmium tetroxide or 3% glutaraldehyde at 4 C. The glutaraldehyde-fixed material was post-fixed in 1% osmium tetroxide. The specimens were next embedded in Epon and subsequently divided into appropriate segments by means of a jeweller's lathe. Sections of the middle turn were prepared using a Cambridge Huxley ultra-microtome, stained with uranyl acetate and lead citrate, and examined in a Philips EM 300 electron microscope.

RESULTS

The cochlear potentials

The dose of ethacrynic acid administered was selected because it was found to be the smallest one which, in the rat, produced gross reduction of the cochlear microphonic potentials (to 10% in approximately 15 min) and particular attention was directed to the early changes since these were of the greatest interest.

With regard to the endocochlear potential, striking effects were invariably found, as in the examples shown in Fig. 1 After a short latent period of 2–3 min, the magnitude of the potential declined at first slowly but then extremely rapidly reaching a minimum of −42 to −50 mV at about 16 min. Thereafter recovery initially was rapid but its rate soon decreased considerably and minor interanimal variations became apparent. However at 60 min the potential had attained approximately +30 mV in all the animals examined and the rate of potential increase became uniformly low for at least the next hour The general pattern of these changes is in good agreement with the experimental records published by Prazma and his co-workers (1972), although these authors do not comment upon the biphasic recovery process.

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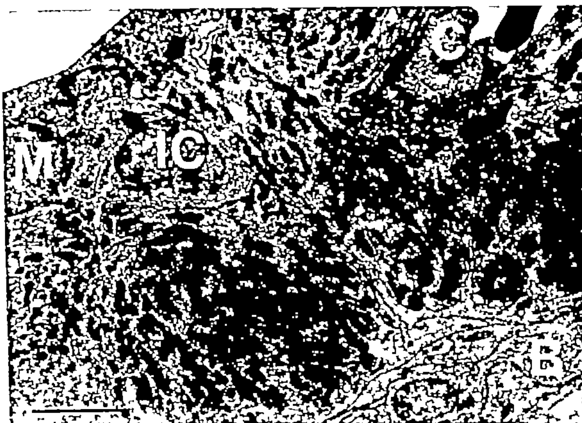


Fig. 3. Stria vascularis 2 hours post-injection. A slight excess of fluid (*arrows*) is visible in the inter-cellular spaces near the endolymphatic surface. *B* basal cell; *C* capillary *IC* intermediate cell, *M* marginal cell, marker = 5 μm.

verstein & Yules, 1971), a number of marginal cell abnormalities have been sporadically observed, including cytoplasmic vacuoles resembling those described by Nakai (1971). The significance of these changes is still completely unknown and, at present, an attempt is accordingly being made to investigate them further

DISCUSSION

Ethacrynic acid, it is now realised, produces a wide range of metabolic effects at the molecular level and it is clearly beyond the scope of this paper to review its action in any detail. However these effects can be broadly divided into two main groups, namely the specific inhibition of a number of enzyme systems (including Na K activated ATPases) and a series of ill-understood abnormalities of membrane permeability

The changes resulting from both types of activity are evident in the endocochlear potential recordings, where the initial rapid decline in the potential is almost certainly the result of enzyme inactivation. The magnitudes of the resulting negative potentials, it will be noted, are of precisely the same order as the negative endolymphatic potentials arising in anoxia and after ouabain administration. In consequence not only would the inhibition appear to be complete in the early stages, but there also seems to be little alteration in the permeability of the cochlear membranes at this time, for investigation has confirmed that these other negative potentials are potassium diffusion potentials and so dependent on the



Fig. 4. Adjacent area to that shown in Fig. 3 at a higher magnification. Marker = 2 μm.

resence of the requisite normal physical characteristics (Johnstone 1965, Kuijpers & Bonting 1970 a).

During the subsequent period, the situation is undeniably more complex and the later marked diminution in the rate of potential recovery is most likely to be due to an increase in permeability at that stage, of at least some portion of the membranes bounding the cochlear duct, with a concomitant decrease in their electrical resistance. In this circumstance, the enzymic processes are unable to maintain the early high rate of potential increase and recovery is thus severely impeded.

In addition, it seems reasonable to expect these permeability changes to be associated with alterations in the endolymphatic composition due to increased diffusion of sodium into and potassium out of the scala media, and this is, in fact, confirmed by the analytical findings. However the ionic constitution remains normal during the initial abolition and early recovery of the normal positive endocochlear potential and such a feature provides further evidence of the absence of any permeability abnormality during this early period, when the inactivation of the enzymes is presumably too fleeting to be accompanied by any manifest anomaly of the cationic concentrations. Moreover by 2 hours the chemical composition has returned considerably towards normal despite the persistence of the membrane effects, as judged by the level of the endocochlear potential. This feature thus provides good evidence of the efficiency of the responsible ion transporting enzyme systems at this time, for the actual values found

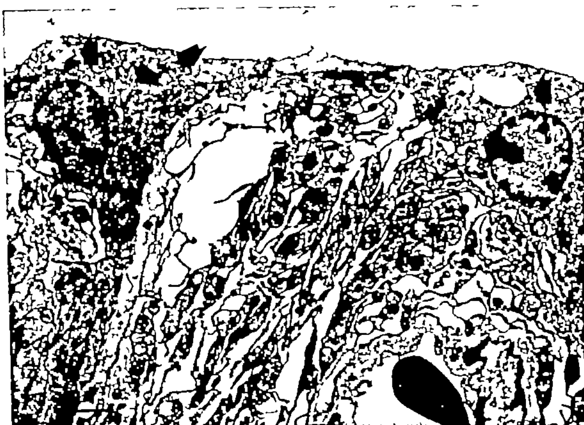


Fig. 5 The stria vascularis 2 hours post-injection in a severely affected animal. In addition to the accumulation of fluid in the inter-cellular spaces, pathological vacuoles are present in the marginal cells (*arrows*). Marker = 2 μm.

differ very considerably from those which, it can be calculated, would arise due to the physico-chemical forces alone.

The reduction in the endolymphatic chloride level and, by inference preservation of the normal bicarbonate concentration is somewhat unexpected. Whether this relative lack of change arises from preservation of the usual chloride permeability or from the functional reserve of the underlying enzyme system can only be a matter of speculation in the present state of our knowledge.

The chemical composition of the general body fluids, as revealed by the perilymph analyses, remained completely normal throughout the period under investigation. This, therefore, completely excludes the possibility that the effect of ethacrynic acid on the endolymph and stria vascularis is secondary to some generalised electrolyte disturbance and so establishes, beyond reasonable doubt, that it must arise from the direct action of the drug upon the cochlea.

The most characteristic and consistent strial abnormality described after single injections of ethacrynic acid has been expansion of the inter-cellular spaces by accumulations of fluid (Quick & Duvall, 1970; Silverstein & Yules, 1971). In the present investigation this expansion is not associated apparently with the initial inhibition of enzyme activity and so the responsible mechanism can hardly be attributed as previously supposed, to primary depression of such activity. Instead, the appearance of the excess inter-cellular fluid coincides with the phase of altered membrane

permeability and would seem accordingly to arise directly from this effect. The preponderance of the distension, in our material, of those spaces situated between the endolymphatic surface and the capillaries adds support to this view and also suggests the excess fluid is removed, to some extent, by its passage into the capillaries.

In summary the broad outlines of the toxic action of ethacrynic acid, as far as it concerns the endolymph, can now be discerned for the first time. Initially the drug produces a short *period of enzyme inactivation which is followed* by a more prolonged phase of altered membrane permeability This commences during the recovery period of the enzymic processes and is associated with the accumulation of fluid in the inter-cellular spaces of the stria vascularis. Nevertheless, it cannot be denied that a great deal of obscurity remains regarding the precise details and complex interaction of the effects produced and a more comprehensive investigation of these fundamental questions is consequently now being undertaken.

Apart from any specific considerations, owever one important matter of general interest remains to be discussed. In their ex remely valuable study of the action of ouabain upon the cochlear potentials, Kuijpers & Bonting (1970 *a*) were able to show that this inhibitor produces a progressive decrease in the endocochlear potential until finally a negative potential, identical in character to the anoxic endolymphatic potential, is attained. The marked similarity between these findings and those resulting from the administration of ethacrynic acid will be immediately apparent but certain crucial differences do exist.

The changes induced by ouabain are slow in onset, largely irreversible and associated with gross ionic disturbances (Konishi & Mendelsohn, 1970). Thus secondary abnormalities, other than the very specific inhibition of the Na K activated ATPase in the stria vascularis, might arguably have a role in the production of the potential alterations. Although ethacrynic acid is far less specific in its inhibitory activity its effects occur very rapidly and other complicating effects, as shown above are delayed until after the initial potential changes and can therefore be excluded from consideration in this respect.

The present investigation, accordingly provides substantial support for Kuijpers & Bonting s (1970 *b*) concept that the normal positive endocochlear potential has two components, the one a secretion potential of about +140 mV due to the activity of the strial *ATPase and the other a potassium diffusion* potential of approximately −40 mV arising from the selective permeability to potassium of some portion of the cochlear duct membranes. This concept is clearly of the utmost importance for our further understanding of the vital physiological functions of these membranes.

RÉSUMÉ

Le potentiel normal endocochléaire fut rapidement remplacé par un potentiel négatif du type anoxique après l'administration d'acide ethacrynique (60 mg/kg) au rat. Au début, la guérison fut rapide mais devint beaucoup plus lente après 30 min. Cependant, la composition endolymphatique chimique resta sans changement jusque 35 min, lorsque se produisit une augmentation progressive de la composition de sodium et une diminution de la composition de potassium, suivie après 1 heure à un retour normal graduel. Ainsi, la drogue causa probablement une inhibition momentanée des enzymes striales et ensuite des anomalies dans la perméabilité de la membrane. L'accumulation caractéristique de fluide inter-cellulaire dans la stria vascularis fut associée avec et semble *survenir de ces changements* de perméabilité. De plus les conclusions supportent fortement la conception que le potentiel endocochléaire a deux composants, un potentiel positif de sécrétion et un potentiel négatif de dispersion de potassium.

ZUSAMMENFASSUNG

Das normale endocochleare Potential bei der Ratte wurde sehr schnell durch ein negatives Potential der Sauerstoffmangel-Art ersetzt nach Verabfolgung von Ethacrynsäure (60 mg/kg). Anfänglich erholte sie sich schnell, nach 30 Minuten wurde die Erholung aber erheblich langsamer Die endolymphatisch-chemische Zusammensetzung blieb jedoch 35 Minuten lang unverändert, worauf[illegible]ne fortschreitende Zunahme in der Natrium- [illegible] nahme in der Kalium-

zentration erfolgte, denen eine Stunde nach Beginn, eine allmähliche Rückkehr zur Norm folgte. So scheint die Droge vorübergehende Hemmung der strialen Enzyme zu bewirken wie auch spätere Anormalitäten in der Membran-Durchlässigkeit. Die charakteristische Anhäufung interzellularer Flüssigkeit in der Stria Vascularis war mit diesen Durchlässigkeitsveränderungen verbunden und schien aus ihnen hervorzugehen. Zusätzlich unterstützen diese Befunde erheblich die Auffassung, dass das endocochleare Potential zwei Komponenten hat: Ein positives Ausscheidungspotential und ein negatives Kalium Diffusionspotential.

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DISCUSSION

D. Hilding: Could the dilated intercellular spaces of the stria represent increased active transport of some ion (perhaps sodium) with associated water movement similar to that which has been observed by Diamond & Tormey in gall bladder epithelium?

J. Stahle: A new antibiotic substance, which was suspected to be ototoxic, has been studied in Uppsala. It is called Bleomycin and belongs to the streptomycin group. As shown first by Japanese colleagues, Bleomycin sometimes has remarkable effect on squamous cell carcinoma. Injected into the middle ear in experimental animals it has produced hair cell damage in the inner ear similar to that seen after streptomycin and other allied drugs. We have also observed vascular changes in the spiral ligament and stria vascularis. These changes ranged from obstruction to disappearance of the vessels. When administered subcutaneously and intraperitoneally to guinea pigs, no ototoxic effects have been observed using current morphological methods. We think that studies of the labyrinthine blood vessels must be included in any investigation of ototoxic effects, as Dr Bosher has so nicely documented.

S. K. Bosher (Reply) to Mr *Hilding*: I think the matter you have raised is of fundamental importance and we are therefore attempting to investigate it further. The restriction of the fluid distension to those spaces situated between the endolymph and the capillaries certainly suggests this to be the pathway of the fluid movement. In addition, our findings indicate that, in all probability, the fluid enters the interstices of the stria by passive diffusion because of the increased membrane permeability but we have no evidence, of course, about the mode of its removal. However, Kimura has demonstrated (in the paper by Silverstein & Yules) that the expansion of the intercellular spaces is still present after 2–3 weeks and such a long persistence seems to me to be more in favour of a passive rather than an active mechanism.

To Mr *Stahle*: I was very interested in your comments for I believe, like you, that it is essential to investigate the effects of ototoxic agents upon all the cochlear structures, including the blood vessels, if we are to fully understand their action. However, the assessment of the relative importance of these varied and inter-acting effects will clearly cause enormous difficulties.

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ZUR SEKRETORISCHEN AKTIVITÄT DER INTERDENTALZELLEN DES LIMBUS SPIRALIS

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Abstrakt Elektronenmikroskopische Untersuchungen am Epithel des Limbus spiralis lassen erkennen, daß in den Zisternen des endoplasmatischen Retikulums und im Golgi-Komplex ein Sekret produziert und kontinuierlich in die Endolymphe abgestoßen wird. Hier verliert sich das zu Bläschen geformte Sekret anscheinend im Fasersystem der Deckmembran. Histochemische Reaktionen zeigen, daß es sich hierbei vorwiegend um Glykoporteide und disulfidbrückenreiche Substanzen handelt, aus welchen sich dann erst im Milieu der Endolymphe die Tektorialmembran unter dem Einfluß von Natriumionen zu ihrer bekannten Gestalt formiert. Morphologische und histochemische Ähnlichkeiten mit dem Sekretionsprodukt des Subkommissuralorganes im dritten Ventrikel des Vertebratengehirnes, dem sog. Reissner'schen Faden, lassen daran denken, daß ebenso wie dieser auch die Deckmembran eine ionenstabilisierende Funktion haben mag.

amphorenartig gestalteten Interdentallen des Limbus spiralis kontaktieren mit dem größten Teil ihrer im Limbusstützgewebe eingebetteten Zelloberfläche mit natriumreicher Perilymphe (v Ilberg, 1968) Ihre hexagonale, endolymphatische Oberfläche zeigt zentral eine trichterförmige Vertiefung auf und ist von einer im Licht und Elektronenmikroskop amorph erscheinenden Grundsubstanz überlagert. Diese Substanz ordnet sich zu feinsten Protofibrillen und läßt sich über die Lippe des Limbus spiralis hinaus in das Lumen der Scala media als sog. Tektorialmembran verfolgen Diese Membran gehört zu den phylogenetisch konstanten Gebilden des akustischen Organs von den niederen Vertebraten bis hinauf zu den Primaten (Schenk, 1963 Wever 1971) Trotz zahlreicher Untersuchungen morphologischer histochemischer und biochemischer Art ist über ihre Entstehung und Funktion außer einigen Theorien bis heute wenig bekannt geworden Wegen ihrer engen topographischen Beziehung zu den Interdentalzellen des Limbus spiralis, zum Epithel des Sulcus internus und zu den Sinneszellen des Corti'schen Organes wurde für jede dieser drei Zellarten bereits eine Mitbeteiligung am Aufbau der Deckmembran diskutiert. Die Arbeiten von Bélanger (1953) Dohlman & Ormerod (1960), Iurato (1962) Voldrich (1967) v Ilberg (1968) Lim (1969 1970), Ishiyama et al. (1970) haben gezeigt, daß die Interdentalzellen an ihrer endolymphatischen Oberfläche Bläschen in das Lumen der Scala media absondern deren Inhalt möglicherweise dem Aufbau der Tektorialmembran dient. Über die chemischen und physikalischen Eigenschaften dieser Stoffe gibt es bislang keine Aussagen. Zwar weiß man, daß die Tektorialmembran neutrale Mucopolysaccharide in großer Menge und zu einem geringeren Anteil auch sauere Mucopolysaccharide enthält, zudem verschiedene schwefelreiche Verbindungen (Schätzle, 1971) ein direkter Nachweis ähnlicher topochemischer Verbindungen im Cytoplasma der Interdentalzellen steht jedoch noch aus.

METHODIK

Zur Untersuchung dienten Meerschweinchen (200–400 g Körpergewicht) Für die lichtmikroskopische Untersuchung erwies sich d e

korporale Perfusion mit dem Fixierungsgemisch nach Bouin oder Allen B. 15 nachfolgender Immersionsfixation und anschließender Entkalkung in EDTA als besonders günstig. Die Paraffinschnitte wurden mit folgenden Methoden angefärbt. Aldehydthioninreaktion nach Paget (1959) Chromalaunhaematoxilin-Phloxin nach Gomori-Bargmann (Pearse, 1960) Paraldehydfuchsin nach Gabe (1956) Alcianblaufärbung nach vorhergehender Oxydation nach Adams & Sloper (1956). Die Reaktionen wurden nach der Vorschrift von Romeis (1968) ausgeführt. Für die lektronenmikroskopische Untersuchung fixier n wir mit 2,5%igem Glutaraldehyd (Karlsm & Schultz, 1965) oder 6 4%igem Gluta- yd (Rewcastle, 1965) durch korporale 'erfusion und anschließende Immersionsfixation zwei Stunden lang. Die Präparate wurden in 1%igem Osmiumtetroxyd (Palade, 1952) .fixiert. Die Einbettung erfolgte in Epon 1? (Luft, 1961) oder im Spurr schen Gemisch 1969). Soweit keine histochemischen Reak ausgeführt wurden, erfolgte Nachkonerung mit Bleicitrat und Uranylazetat. Lokalisation der Natriumionen benützten vir die modifizierte Methode nach Komnick (1963) Fixiert wurde in einem Teil 2%igem ·roantimonat und einem Teil 4%igem Osmiumtetroxyd bei einem pH von 7,6. Zum tronenmikroskopischen Nachweis von alen Mucoproteiden gingen wir nach der orschrift von Rambourg (1967) und Ramrg et al. (1969) vor[1] Zum Nachweis der ransportfunktion zytopempthischer Bläschen die Interdentalzellen injizierten wir 5–10 Minuten vor der Fixation 50–100 µl Thoumdioxyd in die Cisterna cerebello-medullaris. Zur Überprüfung möglicher Mucoproeidstränge in der Endolymphflüssigkeit ent wir dem lebenden Tier Endolymphe und setzten gleiche Mengen von 2%iger Phosolframsäure in 1%igem Amoniumaze tatpuffer bei einem pH von 7,0 zu. Mit einer Mikrokapillare wurde ein Tröpfchen dieses Gemisches auf ein Kupfernetz gegeben, die Flüssigkeit unter Stickstoffatmosphäre angetrocknet und dann im Elektronenmikroskop untersucht.

[1] Wir danken Mrs T Forte, M.D Donner Laboratory nd Donner Pa ilion, Berkeley für ihre hilfreiche Unterstützung bei der Durchführung dieses methodi- chen Abschnittes.

BEFUNDE

Nach Fixation im Bouin schen Gemisch und Entkalkung mit EDTA lassen sich mit der PAS-Färbung nach Hotchkiss und Magnus unterschiedlich große Sekretvakuolen supranukleär im Grundzytoplasma der Interdentalzellen darstellen. In einem Teil der Vakuolen findet man stark PAS-positive kugelige Einschlüsse, deren Übertritt in die ebenfalls sehr stark PAS-positiv reagierende Tektorialmembran in der Regel zu verfolgen ist. Mit Chromalaunhaematoxilin-Phloxin und Aldehydthionin gelingt es, feine, tief blaue Granula im Grundzytoplasma der Interdentalzellen nachzuweisen. Mit diesen hauptsächlich auf Disulfidbrücken (Neurosekret) zielenden Färbemethoden zeigt die Tektorialmembran ebenfalls eine stark positive Reaktion. Nach Glutaraldehydfixation und nachfolgender Osmierung gelingt es allerdings in den Semidickschnitten nicht, die oben erwähnten wasserklaren Sekretvakuolen darzustellen. Dagegen färben sich auch hier mit PAS, Chromalaunhaematoxilin und Aldehydthionin neben der Tektorialmembran zahlreiche Granula im Grundzytoplasma der Interdentalzellen an. Bei der Überprüfung der Natriumverteilung im Bereich des Limbus spiralis und den übrigen Strukturen der Scala media mit der modifizierten Methode nach Komnick ist die Tektorialmembran das einzige Gebilde, welches in auffallender Weise Natriumpyrantimonatniederschläge anreichert. Insbesondere ist festzustellen, daß eben dort, wo im Bereich der ersten Interdentalzellen vor dem Ansatz der Reissner'schen Membran die Grundsubstanz der Tektorialmembran erstmalig licht mikroskopisch auf der Oberfläche sichtbar wird, auch Natriumniederschläge angetroffen werden. Über den epithelialen Zellen



Abb 1 (*a*) Semidünnschnitt durch den Limbus spiralis der zweiten Scalenwindung. Chromalaunhaematoxylin-Phloxinfärbung. Neben der positiven Reaktion im Bereich der Tektorialmembran sind besonders im zentralen Anteil des Limbus spiralis der zu jeder einzelnen Interdentalzelle gehörige Sekretbelag (→) und die scharf gezeichneten positiv gefärbten Interzellularfugen deutlich hervorgehoben. *si* = Sulcus internus; – Scala media, *RM* = Reissner'sche Membran. Fix. Glutaraldehyd; 500 × (*b*) Positive Reaktion einiger Sekretgranula im Grundzytoplasma der Interdentalzellen (→) und der Tektorialmembran. Fix. Glutaraldehyd Aldehythionin. 1 400 × (*c*) Nach Bouin-Fixation ist das Cytoplasma im Gegensatz zur Fixation mit Glutaraldehyd vakuolig aufgetrieben. Intrazellulär stellen sich Kondensate eines PAS-positiven Materials im optisch leeren Grundcytoplasma dar 800

bus, die nicht von der Tektorialmembran werden liegen auch keine Pyroantimonatpartikelchen (Abb 1 2).

Ultrastrukturell weisen die Interdentalzellen typische morphologische Kriterien für sekretorisch aktive Zellen auf So findet sich in der Regel supranukleär ein ausgeprägtes lamelläres System von Schläuchen des endoplasmatischen Retikulums, die einen dichten Ribosomenbesatz zeigen. An ihren Enden schnüren sich Bläschen ab die teilweise noch mit Ribosomen besetzt sind und treten offensichtlich zu dem stets nahegelegenen Golgi-Komplex in enge Beziehung. Von dort aus lassen sie sich mit unterschiedlich dichtem Inhalt bis an die Oberfläche der Interdentalzellen verfolgen. Sie wölben die Zellmembran in Richtung Endolymphe vor ein Vorgang der häufig als mikrovilliartige Zellkonfiguration imponiert. Diese zytoplasmatische Ausstülpungen schnüren sich ab und werden mit ihrer Hilfe in die Grundsubstanz der Tektorialmembran ausgestoßen. Sehr deutlich läßt sich im Elektronenmikroskop eine Beziehung zwischen Grundsubstanz der Tektorialmembran und intrazytoplasmatischen Bläschen erkennen. Nur dort wo im Grundzytoplasma Bläschen zur Oberfläche der Interdentalzellen wandern und in die Endolymphe ausgestoßen werden ist auch die amorphe Grundsubstanz der Tektorialmembran nachweisbar Die am weitesten lateral zum Ansatz der Reissnerschen Membran hin gelegenen Limbusepithelzellen enthalten nur ganz vereinzelt wasserklare zytopemptische Vesikel an ihrer Oberfläche fehlt der amorphe Belag, den man üblicherweise weiter medial auf dem Limbusepithel erkennen kann (Abb 3).

Daneben trifft man im Grundzytoplasma der Interdentalzellen auf eine weitere Art von Zytopempsisbläschen, die sich, wie mehrfach beschrieben, aus der lateralen Zellbegrenzung in das Zellinnere einstülpen, von dort ebenfalls an die Oberfläche wandern und in die Endolymphe entleert werden. Nach Injektion von Thorotrast in den Liquor cerebrospinalis enthalten jene Bläschen bereits nach wenigen Minuten Thorotrastpartikelchen, die man schließlich auch in der Tektorialmembran wiederfindet.

Neben den beschriebenen Zytopempsisbläschen heben sich Vesikel von unterschiedlicher Größe und relativ elektronendichtem Inhalt ab die über das gesamte Zytoplasma verstreut liegen. Ihre enge Beziehung zum Golgi-Komplex läßt auf eine Mitbeteiligung dieses Systems bei der Aufbereitung ihres dichten Inhaltes schließen. Gelegentlich trifft man auch relativ große zytoplasmatische Einschlüsse, *deren membranbegrenzter elektronendichter* Inhalt, sowie die enge Beziehung zu Lamellen des Golgi-Apparates und den dunklen Vesikeln daran denken läßt, daß es sich um eine Sekretspeicherungsform handelt. Unter Anwendung der PA-Chrom Silber methenamin-Methode nach Rambourg (1967) konnten wir in vielen zytoplasmatischen Vesikeln Glykoproteidverbindungen lokalisieren. Ebenso wie diese reagierte die Tektorialmembran stark positiv allerdings auch das Gitter fasernetz des Limbusstützgewebes (Abb. 4).

Mit der Komnick schen Kaliumpyroantimonatmethode gelang es im elektronenmikroskopischen Bereich nicht, im Lumen der Zytopempsisbläschen einen positiven Reaktionsausfall zu erkennen. Dagegen läßt sich anhand benachbarter Zellstrukturen zeigen, daß der zytopemptische Transport von Natriumionen in anderen Epithelien der Scala media möglich ist (positiv im Bereich der Reissner'schen Membran). Auch die perilymphatische Umgebung der Interdentalzellen im Bereich der Huschke schen Zähne enthalt zahlreiche Natriumpyroantimonatniederschläge Sowohl im Lichtmikroskop als auch im Elektronenmikroskop wird sehr deutlich, daß die Tektorialmembran einen besonders starken Reaktionsausfall beim Nachweis auf Natriumionen zeigt. *Die filamentäre Struktur* der Deckmembran ist durchsetzt von zahllosen Pyroantimonatniederschlägen. Im Zytoplasma der Interdentalzellen dagegen lagern ausschließlich die großen elektronendichten membranbegrenzten Sekretpakete an ihrer Oberfläche Natriumpyroantimonat an

Schließlich untersuchten wir noch mit der „negative staining Methode" lebend frisch entnommene Endolymphe und *unfixierte* Tektorialmembran und fanden daß in der Endolymphe zahllose fadenartige Strukturen vorhanden sind, die große Ähnlichkeit mit den Fibrillen der Tektorialmembran haben. Handelt es sich dabei tatsächlich um Glykoproteide, so wäre zu erwarten, daß diese irgendwo im Wandepithel des Ductus cochlearis resorbiert werden, falls sie nicht vorher *enzymatisch aufgelöst wurden. Deshalb* kontrollierten wir mit den oben beschriebenen histochemischen Methoden das Wandepithel des Endolymphraumes und fanden sowohl lichtmikroskopisch als auch elektronenmikroskopisch im Epithel des Sulcus externus und im Bereich der epithelialen Schicht der Reissner'schen Membran einen positiven Reaktionsausfall auf neutrale Glykoproteide (Abb. 5)

DISKUSSION

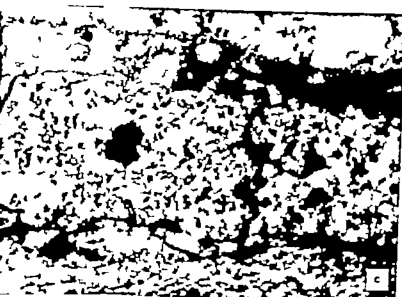
Bereits Voldrich *hatte 1967 gezeigt, daß die* Interdentalzellen rhythmisch ein wasserklares Sekret in die Endolymphe abgeben. Eine Anfärbbarkeit des Vakuoleninhaltes oder des Restzytoplasmas mit PAS gelang jedoch nicht. Auch Iurato (1962), v Ilberg (1968), Lim (1970), Ishiyama et al. (1970) haben auf grund ihrer morphologischen Befunde auf eine sekretorische Funktion der Interdentalzellen geschlossen. Enzymhistochemische Untersuchungen am Limbusepithel (Vosteen, 1960· Gerhardt, 1962 Ishii & Balogh, 1966 Lim, 1970· Nomura & Balogh, 1964



Abb. 2 (*a*) Nach Kalium-Pyroantimonat-Osmiumfixation findet man auf der perilymphatischen Oberfläche der Reissner'schen Membran zahlreiche Niederschläge. Im Endolymphraum fallen lediglich im Bereich des Glykoproteidbelages über dem Limbus spiralis Niederschläge aus. Dort wo das Limbusepithel frei von Glykoproteidbelag ist (→) fehlen auch die Niederschläge. 500×



(*b*) Die Tektorialmembran ist durchsetzt von Natrium-Pyroantimonatniederschlägen. Fix. wie a. 900



(*c*) Ausschnitt eines apikalen Anteiles einer Interdentalzelle im elektronenmikroskopischen Bild. Die Glykoproteidschicht über den Interdentalzellen enthält zahlreiche Natriumniederschläge, während das Grundcytoplasma der Interdentalzellen und die Cytopempsisbläschen frei von Pyroantimonatniederschlägen sind. Im Limbusstützgewebe dagegen sind positive Niederschläge (→) vorhanden. Fix. wie a. 6 400



3. (*a*) Elektronenmikroskopischer Ausschnitt ı der endolymphatischen Oberfläche zweier be- Interdentalzellen. Über der einen Zelle (y) liegt ein grauer Belag mit vereinzelt optisch leeren Membranringen ( ). Im darunterliegenden Cytoplasma erkennt man zahlreiche scharf begrenzte Bläschen mit fein granuliertem Inhalt, die in die Tektorialmembran abgesondert werden. Dagegen zeigt die benachbarte Interdentalzelle ( ) nicht diese scharf begrenzten Bläschen im Grundcytoplasma, dementsprechend fehlt auch der graue Belag auf der endolymphatischen Zelloberfläche. Fix. Osmium Glutaraldehyd, 3 000 (*b*) Die Cisternen des endoplasmatischen Retikulums schnüren an ihren Polen Bläschen (→) ab, welche zur endolymphatischen Zelloberfläche wandern. *M* = Mitochondrium *K* = Zellkern. Fix. wie 3 a. 32 000

1971) bestätigen anhand des Enzymmusters von oxidativen und hydrolytischen Enzymen die Annahme einer Beteiligung dieser Zellen bei einem Sekretionsprozeß.

Allerdings war es bislang noch nicht gelungen über die chemischen und physikalischen Eigenschaften des Sekretionsproduktes eine genaue Aussage zu machen. Die von uns *angewandten histochemischen und histologischen* Untersuchungsmethoden ergaben sowohl im Licht als auch im elektronenmikroskopischen Bereich, daß die Interdentalzellen ein Sekret produzieren, das die gleichen histochemischen Eigenschaften zeigt, wie die Tektorialmembran selbst. Neben der stark positiven Reaktion auf PAS gelang auch der Nachweis von sulfidbrückenreichen Anteilen im Grundzytoplasma der Interdentalzellen. Wir schließen daraus, daß die Tektorialmembran als Sekretionsprodukt der Interdentalzellen aufzufassen ist. Als weiteren Beweis möchten wir die Tatsache anführen, daß im elektronenmikroskopischen Bild das Limbusepithel nur an den Stellen von Deckmembran überlagert ist, wo zytopemptische Bläschen an die Oberfläche ausgestoßen werden. Allerdings erklärt sich aus dem alleinigen Sekre svorgang noch nicht die konstante Konfi- der Tektorialmembran. Es wird ver edenlich diskutiert daß Ionen die Form von Mucopolysacchariden stabilisieren (Davis, *1958 Vilstrup & Jensen, 1954 Jensen & Vilstrup* 1960) Bei der Überprüfung der Natriumverteilung im Bereich des Innenohres konnten wir zeigen, daß im endolymphatischen Kompartment die Tektorialmembran selektiv Pyroantimonatniederschläge anreichert. Da mit dieser Methode nicht nur Natrium- sondern auch Magnesium- und Kalziumionen ausgefällt werden können (Komnick, 1963 Sumi, 1971 Sumi & Swanson 1971 Klein et al., 1972, Forte 1970 persönl. Mitteilungen) muß gefolgert werden daß die Tektorialmembran reich an Ionen dieser drei Elemente ist. Aus den Untersuchungen von Naftalin et al. (1964) geht jedoch hervor daß im Hydrolysat der Tektorialmembran nur



Abb. 4 Mit der PA-Chr-Silber Methenamin-Methode nach Rambourg lassen sich im Grundcytoplasma der Interdentalzellen und im Bereich der Tektorialmembran (*TM*) neutrale Glykoproteide elektronenmikroskopisch nachweisen. Fix. Glutaraldehyd ohne Osmium. 9750× *Inset* Entsprechende Interdentalzelle im Lichtmikroskop nach Chromalaunhaematoxylin-Phloxin-Färbung und gleicher Fixation 1500

sehr geringe Mengen Magnesium und Kalzium ebenso wie in der Endolymphe selbst zu finden sind. Deshalb können wir cum grano salis und unter kritischer Berücksichtigung der methodischen Spielbreite vermuten, daß der Reichtum an Pyroantimonatniederschlägen in der Tektorialmembran ihren hohen Gehalt an Natriumionen widerspiegelt Somit wäre es vorstellbar daß die Glykoproteide der Tektorialmembran in ihrer Funktion als Polyelektrolyte Natriumionen anlagern und daß erst dadurch die Deckmembran ihre Form behält Zum anderen ist zu bedenken, daß durch die Sekretion der Interdentalzellen laufend neue Valenzen frei werden und zur erneuten



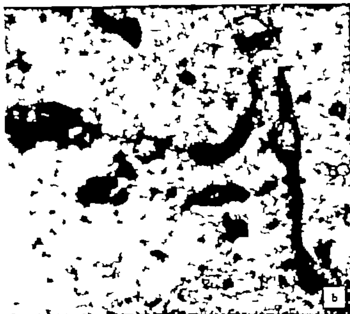


Abb. 5. Negativ staining mit Phosphorwolframsäure von frisch entnommener Tektorialmembran (5 a, 32 000) und Endolymphe (5 b 19 600). In der Endolymphe findet man fadenartige Strukturen ähnlicher Konfiguration wie im Negativbild der Tektorialmembran.

Anlagerung von Ionen zur Verfügung stehen. Unter Berücksichtigung dieser Möglichkeiten könnte man den Glykoproteiden der Tektorialmembran auch eine Funktion als Ionenfänger zuschreiben auf diese Weise wird das Ionenmilieu in der Endolymphe insbesondere im Bereich der Haarzellen konstant gehalten. Änderungen dieses Gleichgewichtes, hervorgerufen durch versiegende Sekretion der Interdentalzellen oder durch ein Überangebot an Natriumionen, müßten zu erheblichen osmotischen Veränderungen im Bereich der Endolymphe führen. Einen morphologischen und funktionellen Beweis für unsere Vorstellungen liefern die Befunde von Voldrich (1968). Dem Autor gelang es zu zeigen, daß nach Ruptur der Reissner'schen Membran und der dadurch hervorgerufenen Durchmischung von Endo- und Perilymphe es zu einer meßbaren Aktivität im Sinne einer

Sekretionssteigerung der Interdentalzellen kommt. Ähnliches Verhalten der Limbusepithelzellen stellte Voldrich (1968) auch nach Beschallung seiner Versuchstiere fest. Nakashima et al. (1971) sowie Suga et al. (1970) konnten nach starker akustischer Stimulation ein Absinken der K^+-Konzentration und ein *Ansteigen des Na-Gehaltes in der Endolymphe* von Meerschweinchen messen. Diese Ergebnisse passen sehr gut in das Konzept einer Abhängigkeit der sekretorischen Aktivität des Limbusepithels vom Na-Gehalt der Endolymphe. Die erhöhte Aktivität der Interdentalzellen könnte als gegenregulatorischer Vorgang bei erhöhter Na-Konzentration aufgefaßt werden und den Versuch darstellen, mit Hilfe des Sekretionsproduktes — entsprechend unseren Befunden — Na^+-Ionen zu binden. Die von uns mit Hilfe der Negativ-staining-Methode aufgezeigten fibrillären Strukturen im Bereich der Endolymphe, die sehr große Ähnlichkeit mit dem Negativ-staining-Bild der Tektorialmembran haben, könnten Abbauprodukte der Tektorialmembran darstellen, die beladen mit Kationen vom Wandepithel des Ductus cochlearis resorbiert werden. Diese Vorstellung knüpft an die Be nde Dohlmans (1971, persönl. Mitteilungen) an, der den Mucopolysaccharidfäden der Endolymphe von Tauben eine Mitbeteiligung bei der Osmoregulation zuschreibt.

Schließlich sei erwähnt, daß aus der vergleichenden Anatomie ein sehr ähnliches sekretorisches Organ bekannt ist. Es handelt sich dabei um das ependymale Subkommissuralorgan am Dach des dritten Ventrikels aller Vertebratengehirne, das als Produktionsstätte für den sog. Reissnerschen Faden gilt. Dieser Faden stellt einen neutralen Glykoproteidkomplex dar, der Zystein, Thyrosin, Tryptophan und weitere biogene Amine sowie Sialinsäure enthält (Bargmann & Schiebler 1952, Sterba, 1969, Sterba & Wolf 1969). Er verläuft durch den dritten Ventrikel, den Aquaeductus Sylvii bis zur Endampulle des Zentralkanals und ist bei allen Vertebraten einschließlich dem Menschen konstant vorhanden. Funktionell wird auch dem Reissnerschen Faden eine Mitbeteiligung bei der Osmoregulation des Liquor cerebrospinalis (möglicherweise Ionenaustauscherfunktion, Sterba, 1969, Arnold, 1969) zugeschrieben. Der Vorgang der Sekretbereitung in den Zellen des Subkommissuralorgans ist licht- und elektronenmikroskopisch genau untersucht und zeigt in vieler Hinsicht Ähnlichkeit mit den Befunden an den Interdentalzellen des Limbus spiralis cochleae.

RÉSUMÉ

Des recherches de microscopie électronique permettent de constater que les citernes du réticulum endoplasmatique des cellules interdentales produisent une substance qui est continuellement excrétée dans l'endolymphe. Il s'agit de substances amorphes et peu visibles en microscopie électronique qui sont entourées par une membrane tendre et forment des vésicules. Ces vésicules semblent se perdre entre les fibrilles de la membrane tectoriale. Des réactions histochimiques font présumer qu'il s'agit principalement de glycoprotéides neutres qui dans le milieu de l'endolymphe forment la membrane tectoriale (sur l'influence du sodium). La ressemblance histochimique et morphologique de la membrane tectoriale avec l'organe souscommissural du 3ème ventricule et son produit la corde de Reissner font penser que la membrane tectoriale est un organe semblable qui possède éventuellement une fonction ionostabilisatrice.

SUMMARY

Electronmicroscopically the cytoplasm *of the inter*dental cells show typical features of secreting cells. An amorphic and less electron-dense substance is produced by the endoplasmic reticulum, packed by the *Golgi-complex into vesicles of different* sizes and are delivered into the endolymphatic space. There they get lost among the fibres of the tectorial membrane. Histochemical reactions allow the conclusion that neutral glycoproteids are the main components of the pinocytotic vesicles as of the tectorial membrane. We assume that in the medium of the endolymph and under the influence of sodium ions the glycoproteids are stabilized and receive the wellknown form of the tectorial membrane. Morphologically and histochemically this kind of secretion of glycoproteids into a body fluid is very similar to the data well known from the so-called subcommissural organ of the 3rd ventricle in vertebrates. The subcommissural organ produces neutral glycoproteids into the CSF which form the Reissner's fibre. Both the tectorial membrane and Reissner's fibre are discussed as having ionic stabilizing properties.

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DISCUSSION

H Spoendlin: It would be interesting to know whether this polysaccharide secretion of the surface

of the interdental cells takes place during the entire adult life at similar rates or whether it is mainly an important process during the development of the tec torial membrane Concerning the histochemical method of Komnick for the demonstration of Na, I do not think that the concentration of the reaction product at certain surfaces is significant evidence of high Na-concentrations at these sides during life Secondary adsorption of histochemical reaction products at any surface is a common phenomenon.

I Friedmann Some of my questions have been touched upon by Drs Engström and Spoendlin. We have studied the spiral limbus of the embryonic mouse and have noted filaments passing from the cells into the membrane of Reissner Laminated bodies have been described in the subcocommissural organ by Wetzstein et al. Similar cellular inclusions were described by Friedmann et al. in the human macula of the utricle of patients operated on for Ménière's syndrome. Do these inclusions indicate some metabolic disorder and have they been observed in the limbus cells?

W Arnold (Antwort) zu Prof *Spoendlin*.

a) Die rege Zellaktivität, erkennbar an der Formation des endoplasmatischen Retikulum, der Golgikomplex, sowie anderer Zellorganellen sprechen für eine aktive Leistung der IDZ. Unsere Ergebnisse zeigen, dass die Zellen am Aufbau der TM maßgeblich beteiligt sind. Es ist anzunehmen (wir untersuchten nur ausgewachsene Tiere) daß die Sekretion das ganze Leben hindurch anhält. Über den Stoffwechsel der TM und ihren Abbau weiß man allerdings noch nichts genaues.

b) Die Komnicksche Methode erlaubt nur eine bedingte Aussage. Deshalb sind Kontrollversuche, Naßwertbestimmung etc., hier sehr wichtig. Es zeigten sich nach Oubainvorbehandlung der Tiere signifikante Änderungen der Niederschlagsdichte im Endolymphraum und im Bereich der Reissnerschen Membran. Insbesondere ist hier der Sulcus internus, Tectorialmembran, Haarzelloberfläche und Oberfläche der Stria vascularis von einem dichten Na-Pyroantimonatbelag überlagert, was ohne Oubainbehandlung nicht erkennbar wird. Dennoch erfordert diese Methode noch einer genauen Überprüfung.

An Prof *Friedmann*.

a) Wir untersuchten nur ausgewachsene Meerschweinchen von 200–400 g Körpergewicht. Fibrilläre, fädige Strukturen, die unmittelbar von der Zelloberfläche der Interdentalzellen abgehen (wie bei der Maus) fanden wir nicht.

b) Im Subcommissuralorgan liegen um die Gefäßkapillaren an der Basis der SCO-Zellen dichte Mucopolysaccharidkomplexe, die sog. periodisch strukturierten Körper Wetzstein Schwink, Stanka u.a. haben darauf hingewiesen und vermutet, daß es sich hierbei um eine besondere Form der Blut Hirnschranke handelt. Im Bereich des Limbusstützgewebes findet man solche Strukturen jedoch nicht. Ähnliche Gebilde liegen in der Regel zwischen den Böttcherzellen, allerdings sind dort wiederum keine Kapillaren.

c) Menschliches Material haben wir nicht untersucht.

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GOLGI STAINS ON THE GUINEA PIG ORGAN OF CORTI

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stract. The Golgi stain has been used to study .g of cochlear and efferent nerve fibers within organ of Corti of the guinea pig. Impregnations the fibers of the olivo-cochlear tract was obtained often than of the cochlear nerve fibers. Some nerve fibers showed branching limited to the terminal end of their spiral traverse.

A large number of studies on the innervation the organ of Corti were made between 1880 nd 1940 by a number of highly competent Among these Cajal (1960), Held (1926), Retzius (1884) and Lorente de Nó (1937) were outstanding. They made their stu- by means of either the silver stains or the Golgi method.

It was the consensus from these studies that separate neurons supplied inner and hair cells. Each inner hair cell was pplied by several short radial nerve fibers, as each outer hair cell received termi- from a number of spiral fibers. The ex spirals (to the outer hair cells) supplied hair cells over a larger area of basilar than the short radial fibers (to the nner hair cells). Lorente de Nó (1937) concluded from his Golgi studies on the rat that spiral fibers often traversed a distance of -third of a coil, and gave off many terminals to outer hair cells along their course.

In the past 30 years, other features of inner ation have been added. Rasmussen (1946) de ribed the olivo-cochlear bundle which sends its axons into the organ of Corti. Through he efforts of a number of investigators (Kimura & Wersäll, 1962, Iurato 1962, Smith & Rasmussen, 1963 Iurato et al., 1968 Smith, in press) some aspects of the course of the bundle and its hair cells are now well-known. By the use of electron microscopy coupled with experimental nerve degeneration, and by means of the acetylcholinesterase stain we have been able to trace the nerve fiber bundles and to distinguish the nerve endings. Yet we know almost nothing about the course of single efferent axons, their length, or the number of hair cells they supply

Electron microscopy has enabled us to visualize single nerve fibers, and the nerve endings on the hair cells. We (Smith & Sjöstrand, 1961) have counted the number of nerve endings on outer hair cells in several locations in the guinea pig organ of Corti. The outer hair cells in the basal coil have fewer cochlear nerve endings than those in the apical coils. Thirty small cochlear nerve endings were counted on a single cell from the third coil. Spoendlin (1966) has found there are about 20 radial nerve fibers terminating on the inner hair cells in the cat cochlea. We (Smith & Takasaka, 1971) have found there are 6 to 10 nerve endings on the inner hair cells of the chinchilla. But, before the present study the best anatomical information available about branching of the external spirals came from Lorente de Nó (1937). Recent neurophysiological studies from Kiang (1965) and others have raised questions about the validity of previous reports because response curves from single nerve fibers are more

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sharply tuned than would be assumed for fibers innervating hair cells distributed over a long length of basilar membrane.

This lack of information is due to several morphological features. the nerve fibers are small (0 1–0 7 microns in diameter) they are unmyelinated they course together tightly packed in bundles composed sometimes of over a hundred fibers (Smith, 1967). It is not possible to trace single fibers if the silver stains are used, because all the fibers are impregnated. It is not practical to follow the fibers by electron microscopy because their pathways are long and devious.

We have used the Golgi stain as one solution to the problem. The Golgi stain has the advantage that only a few nerve fibers in a preparation are impregnated. It is thus sometimes possible to trace the course and ramifications of a single nerve fiber for some distance. We have been able to do this for the guinea pig cochlea. The material presented here is preliminary in nature as the studies are not yet complete. It will be necessary to study many more nerve fibers in different segments of the basilar membrane before any conclusions can be made.

MATERIAL AND METHODS

Twenty-one guinea pigs (42 ears) were used in the study Nineteen were young adults and 2 were newborn animals. All were treated in a similar but not identical manner The rapid Golgi method as described by Valverde (1970) was used. Variations were made in the timing sequence and in the manner in which the organ of Corti was exposed to the impregnating solutions. Most of the ears were prepared as follows:

The animals were anesthetized by Dial with urethane. After decapitation the temporal bones were quickly removed and fixed by intralabyrinthine perfusion with chromeosmium. This is a 0.2 % solution of osmium tetroxide in 2.4% potassium dichromate. The ears were impregnated in this for 7 days. This was followed by a 0 75% silver nitrate solution. Our usual schedule was. 7 days in chrome osmium, one day in silver nitrate, 6 days in chrome-osmium 2 days in silver nitrate, 5 days in chrome-osmium and finally 3 days in silver nitrate. The ears were then dehydrated in ethanol. The entire organ of Corti of each cochlea was then dissected free from the modiolus, and, after completion of the dehydration, mounted on slides to be examined for nerve staining.

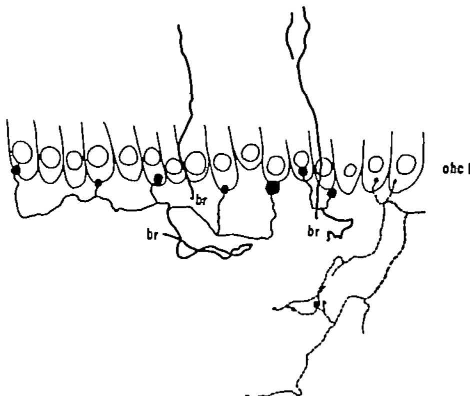
RESULTS

One of the problems that we encountered was the presence of heavy precipitate which interfered with visualization of the stained nerve fibers. A second problem, inherent to Golgi stains, was the unpredictability of the stain. If scala tympani was not opened widely enough to permit a ready diffusion of the impregnating solutions, there was no nerve staining. If the opening was too large, the precipitate could be so great as to obscure the stained nerve fibers. There was no staining at all in 7 ears. Too many nerve fibers were stained to permit analysis of innervation in other ears. The third problem arose from the fragility of the specimens. The prolonged impregnation and soaking in the chrome-osmium and silver nitrate produced a marked brittleness of the tissue. The nerve fibers were easily broken during the dissection dehydration and mounting procedures. Embedding in one of the epoxies may be a solution to this problem. We are at present investigating this.

Nevertheless, despite these drawbacks, we have obtained some interesting information. Both the cochlear nerve dendrites and the efferent axons were stained. Only a few fibers will be described in this preliminary report.

Efferent axons and terminals

The axons and terminals of the olivo-cochlear tract were readily recognizable because of the size of the terminals and their location. The inner spiral and the tunnel bundles were readily



ig. 1 Camera lucida drawing showing two efferent xons crossing the tunnel and terminating on hair ells in the first row (*ohc I*). The fibers were broken *br*) in preparing the specimen. The fibers at right (dashed lines) are cochlear nerve fibers, and the ter minations of the fiber illustrated in Fig. 5. (Guinea pig no. 368 L.) × 275

y distinguished. These latter bundles will not e described at this time.

In many of the ears, large nerve fibers rossed the tunnel and ramified below the first ow of hair cells. When observed as flat dis ected specimens, mounted on a slide, they ad a "grape-arbor" appearance (Fig. 1). The xon usually bifurcated with one primary ranch coursing in an apical direction, the ther toward the base. Single secondary ranches were given off beneath the outer air cells in the first row which terminated as irge rounded bulbs on the hair cell bases. The rminal on each hair cell was usually single ccasionally double nerve endings were seen.

Fig. 1 illustrates 2 such fibers in the third ochlear coil. One axon has only 2 terminals. n adjacent axon has 5 terminals. Both xons supplied only hair cells in the first row The impregnated end bulbs were approximately 2.5 microns in diameter

Another efferent fiber was studied in the fourth coil from another guinea pig. Its terminal ramification covered a much larger seg ment of basilar membrane (0.34 mm). It had nerve endings on 34 outer hair cells in the first row some smaller branches terminated in smaller endings on 6–8 hair cells in the second row There was a network extending over a few hair cells which could not be traced, so that the precise number of terminals could not be determined. There may have been one or two more. Analysis of other axons in the lower part of the second coil from another ear provided additional evidence that some effer ent axons supply more than one row of hair cells.

One axon in the upper part of the first coil

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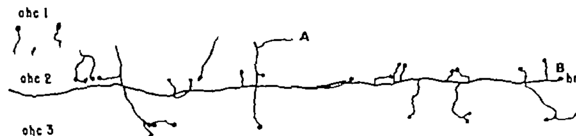
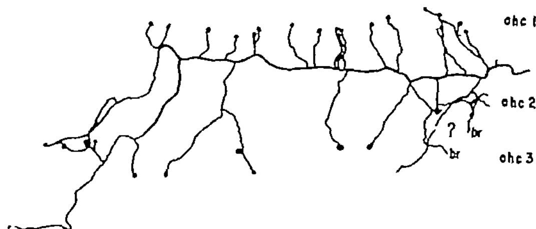


Fig. 4. Camera lucida drawing of terminal ends of two provisional cochlear" nerve dendrites from the lower coil. A fiber terminates on hair cells in the first (ohc 1), second (ohc 2) and third rows (ohc 3). "B terminates only on the second and third rows. (Guinea pig no. 395 R.) 245

second coil. "A" was 0.225 mm in length. hirteen nerve endings could be traced at its ' end (precipitate was present, which have obscured others). These were ted as follows: 3 to the hair cells of the irst row 6 to the second row and 4 or 5 to ne third row B" is another fiber which is .36 mm in length with branching on 0.135 of one end. There were 21–22 nerve end- 12 on hair cells in the second row and on hair cells in the third row This nerve iber had no nerve endings on the hair cells the first row Two other nerve fibers are ted in Figs. 5 and 6. They are from ifferent animals, but both are from the third ochlear coil. The nerve fiber in Fig. 5 is djacent to the efferent nerve fiber in Fig. 1 had 18 or 19 terminals on 12 consecutive air cells in the first row and a fewer number on a few hair cells in the second and third row. It could not be determined where the preterminals at the right ended.

The nerve fiber in Fig. 6 is from the third coil of another animal. It had 23 nerve endings on hair cells in the first row 8 endings on the second row and perhaps 8 endings on the third row The fiber is broken at the right, so that it may have had more nerve endings.

One or two cochleas in which the staining was very dense showed impregnation of numerous nerve fibers within the spiral lamina. These may have been the short radial nerve fibers to the inner hair cells. However the stain and the precipitate were too great in these specimens for analysis. The cochlear nerve dendrites to the inner hair cells were not impregnated in any other specimens.



g 5. Camera lucida drawing of terminal end of a ' cochlear" nerve fiber from the lower hird coil. (Guinea pig no. 368 L.) 280.

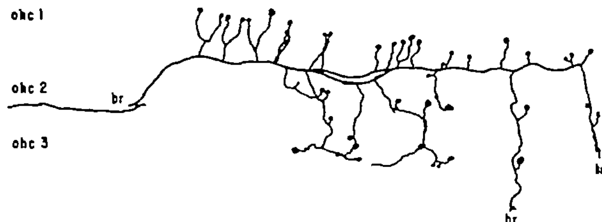


Fig 6. Camera lucida drawing of terminal end of a "provisional cochlear" nerve fiber from the third coil. (Guinea pig no. 389 L.) × 250.

DISCUSSION

It should be emphasized that these are preliminary observations, based on examination of only a few of the 24 000 nerve fibers in the guinea pig cochlea (Gacek & Rasmussen, 1961). Further studies are necessary in order to come to valid conclusions. For example there seems to be an important difference between the cochlear nerve fibers seen in the lower basal coil, and the "provisional cochlear" fiber found in the upper part of the cochlea. Each of the 3 fibers found in the lower basal coil innervated only a single row of hair cells, whereas the apical nerve fibers supplied more than one row and often hair cells in all 3 rows. *Yet our information is* based on 3 nerve fibers stained in the first coil of only one ear and we are not really certain the apical nerve fibers are cochlear nerve dendrites.

Several reasons for the provisional identification of the fibers in the second, third and fourth coils as cochlear have been given. The fact that all the terminals, whether on hair cells from first, second or third rows are of the same diameter seems important, especially if larger efferent terminals have been impregnated in the same specimen If the fibers were olivo-cochlear axons, one might expect the terminals of the first row of hair cells to be larger than those on the second and third rows in the third and fourth coils. On the other hand, some efferent axons may only have large terminals, whereas the terminals on others may be smaller Further the accumulation of globular concentrates of the chrome-osmium seems to be one of the most common artifacts of the Golgi stain. One cannot place too much credence on the size of the end-bulbs. Nevertheless, the comparative measurements of the large and small terminals correspond to the size of efferent and cochlear nerve endings as seen in electron micrographs (Smith & Sjöstrand, 1961).

A more important criterion for the identification of the nerve fibers as cochlear is found *in their mode of branching.* As far as can be determined the parent nerve fibers take a spiral course beneath the hair cells for a variable distance before ramification. This is typical of what we already know about the cochlear nerve fibers from previous studies made by means of the silver stains or Golgi stains. As observed to date, the efferent axons appear to ramify immediately after they cross the tunnel. Often the parent fiber bifurcates and both branches give off secondary branches to the hair cells.

The fact that these "provisional cochlear" fibers send long branches to the neighborhood of Henson s cells is somewhat more difficult to explain Observations made on cochlear

after acetylcholinesterase staining have revealed that AChE-positive fibers (which are efferent) are sometimes found among the Hensen's cells (Iurato & Smith, unpub.). Obviously we need some more positive identification of these nerve fibers.

The variations in the numbers and the locations of hair cells supplied by each fiber is interesting. One efferent fiber in the apical coil supplied more than 40 hair cells, whereas just a few millimeters more basalward (in the third coil) a fiber gave branches to only 2 hair cells, and another fiber to 5. It is possible, but doubtful, that these latter represent incomplete impregnation. It is much more probable that there is a considerable variation in both cochlear and efferent nerve branching. This may be related to place along the basilar membrane. It has been shown previously that there are orderly gradations in numbers of cochlear and efferent nerve endings on the hair cells from basal to apical ends of the guinea pig cochlea (Smith & Sjöstrand, 1961). Possibly there is some reflection of this in nerve fiber ramifications.

One other feature must be emphasized particularly in relation to the efferent axons. We have made no attempts to study branching in the bony spiral lamina. Several of the efferent axons which cross the tunnel may be branches of a single parent axon of the olivocochlear tract which enters the modiolus. It would not be possible to trace the axons in their entire extent from the internal auditory meatus to their terminals by the methods used.

No long spiral fibers which branched along their entire course have yet been seen in the guinea pig. Lorente's (1937) findings that nerve fibers coursed for one-third of a coil giving off branches along the way should be examined in context of the size of the rat's cochlea. The basal coil in the rat is approximately 5 $^1/_2$ mm in length, the second coil is about 3 $^1/_2$ mm long (Békésy 1960). One-third of a coil would be 1–2 mm. The true spiral length of one of the fibers in Fig. 2 could not be measured because it was broken, but the intact portion was 0.7 mm. The length may be comparable to those Lorente found, even though the manner of branching is not. It is possible that we simply have not yet encountered the type of fiber that Lorente described. It is also possible that this type of branching is more prevalent in the rat than in the guinea pig. Other species differences within the cochlea, such as differences in number of efferent terminals per outer hair cell in guinea pigs and chinchilla (Smith & Rasmussen, 1965) and absence of a tunnel bundle in the rat (Iurato, 1961) have already been described. Another species variation would not be surprising.

RESUMÉ

La methode de Golgi est employée afin d'étudier des ramifications des nerfs cochléaires et efferentes dans l'organe do Corti du cobaye. L'impregnation des fibres olivo-cochléaires est obtenu plus fréquemment que celle des fibres cochléaires. Quelques fibres cochléaires ont demontré des branches seulement à leurs extrémités.

ZUSAMMENFASSUNG

Die Verzweigungen der afferenten und efferenten Fasern im Cortischen Organ von Meerschweinchen werden mit Hilfe der Golgi Methode untersucht. Fasern der olivo-cochlearen Bündel liessen sich leichter färben als Cochlearis-Fasern. Die Cochlearis-Fasern zeigen in der Regel erst in den Endabschnitten ihre Verzweigungen.

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DISCUSSION

H Engström The different impregnation techniques give beautiful results occasionally and, in good hands, often. Different authors have reported beautiful results with these techniques and we have used scanning electron microscopy for this purpose. A combination of many methods is necessary to get the full picture of how and where the nerve fibres run inside the organ of Corti. We have found the Maillet method to be very valuable especially for the demonstration of efferent fibres but the technique often demonstrates also afferent fibres in a beautiful manner

H Spoendlin. I was very glad to see Dr Smith's interesting results on the nerve fibre connections of the outer hair cells in the guinea pig. These results are almost exactly the same as we have shown several years ago in the cat on the basis of numerical analysis of basilar and outer spiral fibres and the nerve endings at the outer hair cells. Also in the the cat we find an average spiral extension of the outer spiral fibres of 0 6 mm with only terminal branching and nerve endings to about 10 outer hair cells. (Spoendlin, 1970 In: Frequency analysis and periodicity detection in hearing (ed. R. Plomp & G F Smoorenburg. A W Sijthoff Leiden, Holland). It is important that the findings in the cat have now been confirmed in the guinea pig. This allows us to consider it as a basic innervation principle rather than only a species specific innervation pattern.

Mrs *Smith* (Reply) to Mr *Engström* and M *Spoendlin.* The more different kinds of techniques which are used on the problem, the more quickly will we reach a solution. It is important to close the gap between structure and physiology as rapidly as possible

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WEITERER BEITRAG ZUR ÄTIOLOGIE DER PRESBYACUSIS

J Krmpotić-Nemanić, G Nemanić und I. Kostović

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Abstrakt In der Voraussetzung, dass die Ursache der Altersschwerhörigkeit in einer progressiven Knochenablagerung in der Gegend des Tractus spiralis mit anschliessender Atrophie der Nervenfasern liegt, haben wir auch andere Öffnungen für die Nerven an der Schädelbasis untersucht. Wir konnten feststellen, dass es mit dem Alter auch im Bereich der anderen Öffnungen zur Knochenablagerung, die zur Verengung derselben führt, kommt. Dieser Vorgang ist für einige Manifestationen in der Funktion dieser Nerven verantwortlich. Wir haben versucht, dies auch im Tierexperiment an Ratten zu bestätigen.

Vor fast 15 Jahren haben Šercer und ich die erste Arbeit über die Ätiopathogenese der Altersschwerhörigkeit veröffentlicht. Die ersten Befunde haben sich auf die Untersuchungen an mazerierten Schläfenbeinen der grossen Schädelsammlung von Perović in Zagreb bezogen. Diese Sammlung umfasst 1 300 Schädel vom Fetalleben angefangen bis zum 90 Lebensjahr An diesen Präparaten haben wir eine mit dem Alter progressiv fortschreitende Knochenablagerung am Boden des inneren Gehörganges, die zur Verengung und endlich zum Schwund der siebförmigen Öffnungen im Tractus spiralis foraminosus führt, gefunden. Die Knochenablagerung fand zuerst in dem der Basalwindung entsprechenden Teil des Tractus statt und schritt gegen die Modiolargegend fort. Die Verengung bzw der Schwund der Öffnungen im Tractus muss durch Kompression zur progressiven Atrophie der Akustikusfasern geführt haben.

Die Befunde an mazerierten Schläfenbeinen habe ich an den Schläfenbeinserienschnitten bestätigen können. Die histologischen Untersuchungen habe ich an 114 Schläfenbeinen von 57 Individuen im Alter vom Neugeborenen bis zum 90 Lebensjahr an der Sammlung von Prof Lindsay im Otologischen Laboratorium der Universität in Chicago sowie an 40 Schläfenbeinen von 20 Individuen aus der Sammlung von Prof Kelemen (1969) in der Otologischen Foundation in Los Angeles und endlich an eigenen Schnittserien im Anatomischen Institut in Zagreb durchgeführt. Die Präparate waren beiderlei Geschlechts. Für die Mehrzahl der Individuen lag entweder ein Audiogramm oder die Krankengeschichte vor so dass die Befunde am Knochen mit den klinischen Befunden verglichen werden konnten.

Die Knochenapposition im Bereiche des Tractus spiralis ging einige Phasen durch. Zuerst fand man straffes fibröses Bindegewebe, das im polarisierten Licht Doppelbrechung zeigte. Dann wurde in dasselbe Osteoid abgelagert, das später verkalkte. Auch Gussen beschreibt den Verschluss der vaskulären Kanäle in der knöchernen Ohrkapsel, durch Ablagerung vom amorphen sich blau färbenden Material in das Bindegewebe um die Gefässe. Dieses Material wird später kalzifiziert. Sie hat das kalzifizierende Material mit dem fortschreitenden Alter immer häufiger gefunden. Das Material komprimierte die Gefässe Diese Veränderungen hat sie in grösseren Mengen in der Schneckenkapsel und in der Gegend des Meatus acusticus internus gefunden. Die neugebildete verknöcherte Masse war acellulär

Max Meyer (1923) hat das Zustandekommen der sog durchbohrenden Kanäle in der Labyrinthkapsel von menschlichen Feten und Jungkindern beschrieben. Er hat dabei an histologischen Schnitten ebenfalls das Wachstum des Knochens in die Dicke am Hauptgefäss durch Osteoidablagerung im Bindegewebe mit Osteoblasten gefunden.

Die Knochenablagerung im inneren Gehörgang spielt sich im Bereich des endostalen Knochens ab aus dem die siebförmigen Formationen und der Modiolus entstehen. Die Verknöcherung des Modiolus erfolgt zuerst in Form einer netzförmigen Ablagerung von Kalk in das Bindegewebe, das die Nervenstränge umhüllt Die Verknöcherung schreitet von der Basis gegen die Spitze fort.

In diesem Zusammenhang wollten wir folgendes feststellen

I Ist diese Knochenablagerung im Tractus spiralis ein isolierter Vorgang im menschlichen Körper oder gibt es auch andere Stellen an der Schädelbasis bzw am Knochensystem überhaupt, wo es zur Verengung bzw zum Verschluss der Nerven- oder Gefässöffnungen im Knochen kommt?

II Warum wird die Basalwindung zuerst befallen?

III Ist die Knochenablagerung die Ursache [o]der die Folge der Atrophie und des Schwun[des] der Nervenfasern?

IV Wie verhält sich ein knöcherner Nervenkanal wenn der Nerv im Experiment durchtrennt wird?

Um die erste Frage zu beantworten untersuchten wir 1) andere Bereiche der Schädelbasis, wo die Nervenfasern ebenfalls durch ein System von siebförmigen Öffnungen hindurchtreten u zw die beiden vestibulären Areen und die Lamina cribrosa, 2) die Nerven bzw Gefässkanäle der Schädelbasis u. zw den Canalis rotundus, das *Foramen ovale* das Foramen stylomastoideum, den Canalis N hypoglossi und das Foramen spinae und 3) die Foramina intervertebralia in bezug auf die Osteophytenbildung der Wirbelkörper

Aufgrund dieser Untersuchungen die alle im Rahmen unseres Institutes durchgeführt wurden, konnten wir folgendes feststellen.

1) Die Knochenablagerung findet auch in den vestibulären Areen statt u. zw intensiver in der sakulären als in der utrikuloampullären Gegend, was sowohl an mazerierten Präparaten als auch an histologischen Schnitten bestätigt werden konnte. Diese Knochenablagerung könnte für einige Alterserscheinungen im Gleichgewichtsorgan verantwortlich sein (Presbyostasis). Kelemen hat bei einem totgeborenen Hydrocephalus (ohne Anomalien des Ohres) Exostosen im inneren Gehörgang um die Äste des N VIII für den Sacculus gefunden Er äussert die Möglichkeit, dass dieselben Störungen in der vestibulären Funktion hervorrufen könnten. Die Öffnungen der Lamina cribrosa verengen und verschliessen sich allmählich mit dem Alter in posteroanteriorer Richtung, was für die Altersstörungen des Riechsinnes verantwortlich sein könnte (Presbyosmie)

2) Pećina M. hat die Altersveränderungen des Canalis rotundus und des Foramen ovale am Keilbein durch welche der II bzw III Trigeminusast durchtreten am grossen Material unseres Instituts untersucht. Er konnte feststellen, dass der Canalis rotundus bei den Frauen im Durchschnitt enger ist und dass dessen Durchmesser mit dem Alter in beiden Geschlechtern um etwa 0,4 mm abnimmt (von 3,37 im 11 –20 Lebensjahr auf 2,92 im 80 90. Lebensjahr). Das Foramen ovale ist enger auf der rechten Seite und im weiblichen Geschlecht und verengt sich ebenfalls allmählich in beiden Geschlechtern mit dem Alter Diese Altersverengung der beiden Öffnungen könnte für die Trigeminusneuralgie im mittleren und höheren Alter verantwortlich sein.

Većerina (1972) hat an demselben Material auch eine signifikante Verengung des *Foramen stylomastoideum*, des Foramen spinae und des Canalis N hypoglossi mit dem Altern gefunden. Das Foramen stylomastoideum ist bei den Frauen im Durchschnitt enger als bei den Männern und wird im Alter in beiden Geschlechtern progressiv enger Der Prozess

ist im Alter etwas intensiver bei den Männern. Die Verengung wird besonders ausgeprägt im vierten Dezennium. Auch an den anderen erwähnten Öffnungen tritt die Verengung mit dem Alter ein, beim Foramen spinae im dritten und beim Canalis N. hypoglossi schon im zweiten Dezennium. Nach dem fünften Dezennium ist die Verengung des Foramen spinae intensiver bei den Frauen. Während die Verengung am Foramen stylomastoideum und Foramen spinae konzentrisch ist, wird der Canalis N. hypoglossi durch Stachelbildungen verengt. Diese Verengungen könnten für einige Störungen im Bereiche der entsprechenden Nerven und Gefässe verantwortlich sein.

3) Ähnlich wie die Stachelbildung am Canalis N. hypoglossi kommt es auch zur Osteophytenbildung an den Wirbelkörpern und zur anschliessenden Verengung im Bereiche der durchtretenden spinalen Nerven und Arterien, was zu Störungen in den betreffenden Versorgungsgebieten führt.

Die Lage der Schnecke im Raum und folglich auch die Neigung derselben gegen den Meatus acusticus internus wechselt nach Alexander im Laufe der Entwicklung. Nach Alexander (1902) schliesst die Ebene des hinteren Bogenganges mit der Ebene der Schneckenbasis am Neugeborenen nach oben einen Winkel von 25° ein, am Erwachsenen hingegen beträgt der Winkel nur 9°. Am Neugeborenen sieht die Schneckenspitze nach vorne und abwärts und am Erwachsenen nur nach vorne, so dass sich die Schnecke postembryonal aufzurichten scheint. Da zur selben Zeit der innere Gehörgang beim Erwachsenen länger, sein Eingang enger und die Knochenwand des Gehörganges durch subperiostale lacunäre Knochenresorptionsherde und Anlagerung von Knochenlamellen (Meyer 1923) zackig und buchtig wird, bildet sich in der Mehrzahl der Fälle eine mehr oder weniger tiefe Bucht zwischen der unteren Wand des Gehörganges und der Basalwindung der Schnecke, die am tiefsten unten zu liegen kommt. Die Zirkulation des Liquors müsste



Fig. 1

in dieser Bucht bedeutend verlangsamt sein, was zu einer Konzentration der Liquorbestandteile führt. Dieselbe könnte für die intensivere Osteoid- bzw. Knochenablagerung in dieser Gegend des Tractus verantwortlich sein (Fig. 1).

Um die dritte Frage beantworten zu können, u. zw. was primär ist, die Knochenablagerung oder die Nervenatrophie, haben wir solche Fälle ausgesucht, wo es bestätigt war, dass es sich um eine primäre Atrophie des Nerven handelte. Einen solchen Fall haben wir an den histologischen Schnitten prüfen können, wo die Nervenöffnungen offen geblieben sind, obwohl der ganze Akustikus 40 Jahre vor dem Tode verlorenging. Als den zweiten Fall können wir denjenigen von Fisch (1971) erwähnen, wo etwa 3 J. nach der Atrophie des N. VIII der Meatus noch immer breit blieb, obwohl er nur den N. facialis enthielt. Auch diejenigen Fälle, wo die Osteoidapposition um die Nervenbündel in die Lichtung des inneren Gehörganges hinein stattfindet, sprechen für eine primäre Knochenapposition. Man könnte auch diejenigen Fälle hinzufügen, wo sich knöcherne Zylinder um die Arterienäste im Fundus bilden und die wir sowohl an macerierten als auch an histologischen Präparaten gefunden haben. Die Arterien waren funktionsfähig und von knöchernen Manschetten, die in die Funduslichtung hervorragten, umgeben.

Wir haben in unserem Institut, im Rahmen einer Magisterarbeit (Ciglar I.) folgendes Experiment durchführen lassen. An 31 Ratten (17 junge von 2–3 Monaten und 14 alte von 1–2 Jahren) wurde der rechte bzw. der linke N. opticus durchschnitten. Drei Monate nach der Operation wurden die Tiere geopfert und

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Večerina (1972) hat an demselben Material auch eine signifikante Verengung des Foramen stylomastoideum, des Foramen spinae und des Canalis N. hypoglossi mit dem Alter gefunden. Das Foramen stylomastoideum ist bei den Frauen im *Durchschnitt enger* als bei den Männern und wird im Alter in beiden Geschlechtern progressiv enger. Der Prozess

Mrs *Krmpotić* (Reply) to Mr *Jongkees*. With my remark concerning the narrowing of the facial canal and Bell's palsy I meant that may be this narrowing could cause the spasm of the arteries in th foramen which is considered by some as being the cause of the Bell's palsy

To Mr *Fisch*. I am ery grateful to Mr Fisch for his discussion and for his remark about the contents of protein in the liquor in the region of the internal auditory meatus. His investigation and his idea of decompression of the internal auditory meatus are in complete accord with our idea concerning this problem.

die Nervendurchtrittsstelle an der operierten mit derjenigen an der nicht operierten Seite, die uns als Kontrolle diente verglichen Obwohl der Nervenkanal auf der einen Seite leer war fand doch keine Knochenapposition statt Bei alten Ratten waren die Nervenkanäle auf der operierten und nicht operierten Seite gleich gross. Bei jungen Ratten fand ebenfalls keine signifikante Verengung statt obwohl eine Verengungstendenz angedeutet wurde Dies würde etwa den neuesten experimentellen Untersuchungen von Sarnat Shanedling über Verengung der Orbita nach der Exenteration bzw der Enukleation des Augenapfels entsprechen.

Weitere experimentelle Untersuchungen in diesem Sinne sind im Gange.

RÉSUMÉ

Supposant que la cause de la presbyacousie est une apposition osseuse progressive dans la région du crible spiroide suivie d une atrophie des fibres nerveuses nous avons examiné aussi les autres trous nerveux de la base du crâne Nous avons pu constaté qu'à l'âge avancé on trouve une apposition osseuse aussi dans la région des autres trous de la base résultant en leur étrécissement. Ce procédé est responsable pour certaines manifestations dans la fonction de ces nerfs. Nous avons essayé aussi de prouver ces faits par des expériments sur des rats.

SUMMARY

Supposing that the cause of presbyacusis is a progressive bone apposition in the region of the spiral tract with consecutive atrophy of the nerve fibres, we investigated also the other nerve openings in the base of the skull. We have found that in advanced age bone apposition also takes place in the region of other nerve openings which become narrower This fact is also responsible for some manifestations in the function of these nerves. We also tried to prove our point in some experiments in rats

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DISCUSSION

L. B W Jongkees: Je félicite Mme Krmpotić de la ténacité avec laquelle elle continue de fortifier sa theorie et j'accepte aussi comme très probable que le trousstylomastoidien devient plus petit avec l'âge Hélas, je ne peut pas la suivre Si elle pense que ce phénomène pourrait être à base de la paralysie de Bell. Dans cette maladie le nerf n est pas comprimé par l'os mais par la gaine nerveuse qui, dans la partie verticale ne contient pas de fibres élastiques.

U Fisch. I would like to support one observation of Mrs Krmpotić concerning the possible role of a disturbance in the circulation of the cerebro-spinal fluid in the inner meatus in the production of deafness. We have measured the protein content of the meatal c.s.f in progressive sensori-neural deafness and found an abnormal value sometimes of more than 80 mg This observation has a practical significance since we are able to-day to improve surgically the circulation of c.s.f in the internal auditory meatus.

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SNORING AND PRESBYACUSIS

M. Pražić

From the E.N.T. Department University of Zagreb Zagreb Yugoslavia

Abstract. The pathophysiological mechanism of snoring is briefly explained. The results of spectroscopic analysis of snoring are given. The analysis has shown some standard types of snoring. The parallelism between snoring and noise is pointed out. The audiograms of all examined snorers showed the presbyacoustic reduction of hearing.

Snoring is such a common and harmless phenomenon that one wonders whether to categorize it as a pathological manifestation or not.

A small number of scientific papers written on the phenomenon of snoring have now been published. The only one I came across was the Presidential Address under the title "Snoring" given by J G Robin at the Laryngological Section of R.S.M. in Great Britain in 1967 but he only dealt with secondary pathological complications and troubles caused by snoring. A number of other authors discussed this phenomenon in rather general terms, considering it as being a plain fact that should be prevented. Not a single one tried to find the real cause of snoring.

Nevertheless, a number of paramedical papers written on this phenomenon can be found.

The usual opinion is that mainly human beings snore especially those above 40 years. But the fact is that younger males and even elderly women snore too. Some people snore stronger some milder Some snore during the whole night, some periodically Some snore loud, and some very loud.

Special societies of snorers have been founded in several countries concerned solely with the problem how to construct such a device which would awake the snorer immediately when he starts snoring. But until the present day no such device has been constructed that would prevent snoring

At the meetings of the Collegium in Edinburgh and Lyon some years ago I talked about the pathophysiological mechanism of snoring. This time I will talk about the results of the audiological analysis of snoring and its acoustic qualities.

Intensity of snoring depends on the degree of dryness both of the mucous membrane of the soft palate and of the uvula. Dryness of the mucous membrane of the soft palate and of the uvula depends on the lessening of secretion of mucin from the seromucinous glands in the submucous layer of the upper respiratory tract. The lessening of secretion of mucin is caused by the changed or interrupted neurovegetative impulses of the glands. Since the secretion of mucin falls gradually the seromucinous carpet at the epithelial surface becomes serous, i.e. watery During the respiration the strong and warm stream of air dries and stiffens the soft palate and uvula. They lose their elasticity and start vibrating First they vibrate moderately and with mild intensity Later on, the intensity of vibrations grows stronger

The measuring of the intensity of snoring shows a relatively broad variety There are snorers whose intensity of snoring reaches the level of 70 dB. (Measuring was performed at the distance of 25 cm from the mouth of the

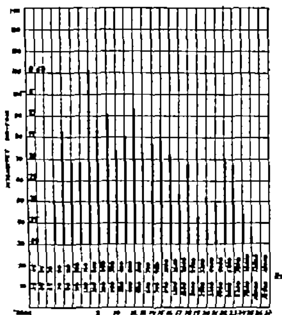


Fig. 1

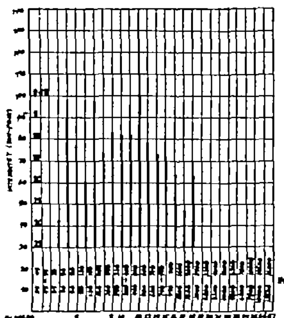


Fig. 2

) Some snorers even reach the level of dB.

The frequency analysis of snoring shows in ng results. The mechanism of snoring is er similar to the mechanical elements of ...ing of the esophageal voice Therefore the and the amplitude elements of snor have similar components.

There are several types of snoring. The first is sonorous snoring that ranges from 60–10 000 c.p.s. (Fig. 1) The second type is not so sonorous as the first and therefore this seems deep. Here the range of frequencies reaches from 60 up 2 000 c.p.s only (Fig. The *third, fourth* and *fifth* type are *more* sonorous. Here the range of frequencies cov the field from 200–8 000 c.p.s. They are ly similar but in many details they are different (Figs. 3–5)

The effects of sonority depth and height snoring depend not only on the range of frequencies but also on the amplitude variations of single segments of frequencies. These ons reach as much as 30 dB in some

All the cases of snoring that I examined (there were altogether 17 snorers), were male persons above 60 years. Only the range from 60–10 000 c.p.s. was analysed. The analysis did not cover the infrasound range, or the range of vibrations. The reason for this lack of analysis lies in the technical field. It is very dif

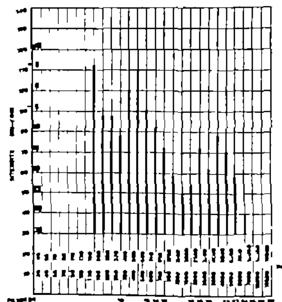


Fig. 3

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Intensity of snoring depends on the degr... of dryness both of the mucous membrane ... the soft palate and of the uvula. Dryness ... the mucous membrane of the soft palate a... of the uvula depends on the lessening of secr... tion of mucin from the seromucinous gla... in the submucous layer of the upper respir... tory tract. The lessening of secretion of muc... is caused by the changed or interrupted neuro... *vegetative impulses of the glands.* Since th... secretion of mucin falls gradually the sero... mucinous carpet at the epithelial surface be... comes serous, i.e. watery During the respira... tion the strong and warm stream of air dr... and stiffens the soft palate and uvula. The... lose their elasticity and start vibrating Fir... they vibrate moderately and with mild inten... sity Later on, the intensity of vibration... grows stronger

The measuring of the intensity of snori... shows a relatively broad variety There are snorers whose intensity of snoring reaches the level of 70 dB (Measuring was performed at the distance of 25 cm from the mouth of the

nal auditory ductus. In this way one can ex plain some of the presbyacoustic reduction of hearing.

If one accepts that the majority of elderly snore and if one takes into considera on that the snorer snores every night for several hours, the intensity of snoring being 80 or above 80 dB, combined with the vibrations, there is a completely new etiological factor for presbyacusis. The snorer snores every night for years, which means that he is exposed to a kind of noise. Therefore a snorer be compared to a worker in a noisy fac y

Amongst the etiologic factors that can presbyacousis one must therefore take nto consideration snoring as a primary fac too.

RESUMÉ

On donne un exposé bref du mécanisme du ronfle Puis on donne des résultats de l analyse spectro- du ronflement concernant les variations en fréquence et en amplitude. L'analyse montre quelques types standardisés du ronflement. On indique le pa- llélisme entre le ronflement et le bruit et on sou- ligne les faits concernant l'effet nuisible du bruit sur l'ouïe. On présente des audiogrammes tonaux des ron- fleurs et, se basant sur ces audiogrammes, on montre une liaison étiologique entre le ronflement et la pres-

ZUSAMMENFASSUNG

Der pathophysiologische Mechanismus des Schnarchens im kurzen ist dargestellt. Nachdem sind die Resultate der spektroskopischen Analyse des Schnarchens mit den Frequenz und Amplitude-Variationen gezeigt. Analyse zeigt einige Standard-Typen des Schnarchens. Der Parallelismus zwischen Schnarchen und Lärm wird betont sowie einige Tatsachen über den schädlichen Effekt von Lärm auf das Gehör. Eine Serie von Audiogrammen vom Schnarchen wird gezeigt und auf Grund dieser Audiogramme wird eine etiologische Kausalität des Schnarchens mit der Entstehung der Presbyakousis angenommen.

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RELATION OF STRUCTURAL DAMAGE TO EXPOSURE TIME AND INTENSITY IN ACOUSTIC TRAUMA

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Abstract In order to overcome the difficulty to obtain a survey evaluation of the entire cochlea as well as an ultrastructural examination of selected areas of the same ear we used a new technique for combined surface preparations and EM studies without the risk of damage by mechanical preparation. Exposure intensities were varied from 100 to 140 dB and exposure times from 30 sec to one week. The relations between exposure time and extent or type of damage on one hand and between exposure intensity and damage on the other hand were worked out at different intensity levels. Above 120–130 dB exposure intensity direct immediate structural damage occurs regularly in various degrees, depending mainly on exposure intensity whereas in lower intensities delayed phenomena are predominant, depending mainly on exposure time

In order to study appropriately the structural damage in acoustic trauma a new technique s used for the preparation of cochlea, al- ving a total surface evaluation of all turns well as light and electron microscopic examinations at any magnification of any desired area of the same specimen. The findings can easily be documented at every step and the risks of mechanical artefacts due to the preparation are reduced to a minimum

The intact cochlea, opened only at the round and oval window is fixed and embedded as a whole in a new low viscosity epoxy resin (Spurr). After polymerisation the embedded cochlea is cut in two halves with a 0 1 mm thick circular saw under a preparation microscope From the two cochlear halves horizontal slices of each cochlear turn are excised and used directly for surface evaluation (Fig. 1). Selected areas of these cochlear turn slices are then dissected out and used for semi-thick and ultrathin sections for conventional light and electron microscopic examination (Spoendlin 1972) A somewhat different procedure aiming at the same final goal has been reported by Bohne (1972) and by Engström (1972)

In the present experiment 110 guinea pigs were exposed to a wide band noise at intensities between 110 and 140 dB and with exposure times between 30 sec. and 1 week. The animals were sacrificed either immediately after the exposure or after a survival time of 3 weeks and 3 months.

At exposure intensities of 130 dB severe structural alterations are found immediately after the exposure Even after 30 sec exposures to 140 dB the organ of Corti was usually entirely missing in a small area of the lower second turn leaving only the bare basilar membrane with the spiral vessel and the tectorial membrane (Fig 1). This zone of missing organ of Corti is sharply limited on both sides against regions of more or less intact structures showing different degrees of distortion. Quite frequently the organ of Corti is not actually missing but roughly disintegrated with ruptures of the reticular membrane or pillar heads, dislocation or expulsion of sensory cells, disconnection of the organ of Corti from the basilar membrane and the trabecula and a complete loss of the tympanic lamina (Fig. 2). Such drastic primary alterations lead necessarily to a complete and permanent loss

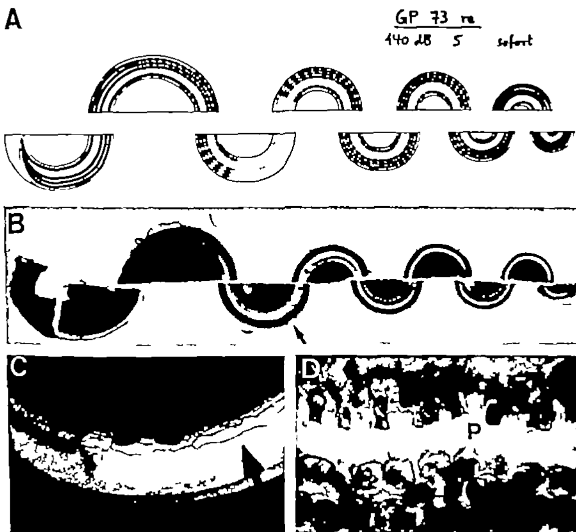


Fig. 1 (A) Diagrammatic representation of the sur preparation of the cochlea depicted in (B). Thick interrupted lines represent areas of distortion whereas thin interrupted lines represent areas of completely missing organ of Corti. (B) A total view of a surface preparation of a guinea pig cochlea immediately after an exposure to 140 dB for 5 minutes. That the organ of Corti is completely missing in the upper basal and lower second turn is clearly seen (*arrow*). (C) Higher magnification of a portion of the upper basal turn of the cochlea in (B). In the region where the organ of Corti is entirely missing the spiral vessel is still clearly visible (*arrow*). There is an abrupt transition from entirely missing organ of Corti to a more or less intact organ of Corti on the left. (D) Detail of an organ of Corti showing heavy distortion, respectively disintegration. The outer hair cells (*H*) are irregularly swollen and distorted. The pillar heads (*P*) are for the greater part entirely missing. (Compare Fig. 2).

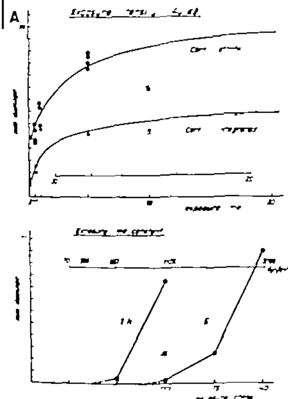
of all cellular elements of the organ of Corti. These alterations are obviously the consequence of a direct mechanical damage not only because of their appearance but also because of the very short exposure times of a few seconds needed to produce them.

A quite different type of lesion is found after longer exposures to lower intensities, below 120 dB. Single outer hair cells degenerate amidst entirely normal cells, scattered over large distances. The primary changes are always confined to the sensory cells, which are swollen with a vacuolization of the cytoplasm and mitochondrial degeneration and are fi-



Fig .. Low magnification, electron microscopic picture of an organ of Corti in disintegration corresponding to the area depicted in Fig. 1D The pillar heads (*P*) are ruptured and the whole organ of Corti is burst open towards the endolymphatic space The outer hair cells (*oH*) and the inner hair cells (*iH*) are heavily distorted and partly exposed in the endolymphatic space The fine cytological elements as well as the internal spiral fibres do not show much significant alteration. The tympanic lamina is almost entirely missing and only the spiral vessel (*T*) remains in place The whole organ of Corti seems to be disconnected from the basilar membrane and the habenula region. The tectorial membrane (*M*) is essentially normal.

nally completely disintegrated whereas the nerve endings still remain intact at this stage Scattered degeneration occurs also to a much smaller degree spontaneously in normal animals, which means that a normally occurring process is merely enhanced by acoustic over stimulation. For these changes as well as for the frequently observed swelling of the dendrites to the inner hair cells (Spoendlin, 1970 1971) a purely mechanical mechanism is excluded and metabolic disturbance such as metabolic exhaustion is the most likely cause



...ig. 1. (A) Diagram showing the relation between the extent of damage (in mm) and the exposure time ...a constant intensity of 140 dB. The upper curve ...lates to the entire area of distorted organ of Corti ...hereas the lower curve relates to the area where the ... is entirely disintegrated or missing. After a very ...p initial rising phase the curves flatten out to be...come almost horizontal. If time scale is taken loga...rithmic (smaller inset scale) the curves become more ...less straight, slowly rising lines (interrupted lines). (B) Diagram representing the relation between the ...nt of damage (in mm) to the exposure intensity ... constant times of one hour (left curve) and 5 ...minutes (right curve). Above a certain critical level ...hese curves rise with increasing steepness. If the ... intensity is expressed in a linear manner as ...n dyn/cm² as shown in the upper inset scale with ... corresponding sound pressure values, the curve ...interrupted line) becomes almost straight.

At exposure intensities of 120–130 dB the ...al alterations consist mainly of different ...egrees of distortion of the hair cells, which ... be attributed to a mechanical as well as to metabolic disturbance. The very typical out...ardbending and fusion of the sensory hairs ...of the inner hair cells is found even after ...latively mild exposures and usually extends apicalwards far over the main damage zones as the only significant structural alteration (Spoendlin, 1971). Fusions of sensory hairs appear to be a rather general and unspecific response to many different types of damaging factors such as intoxication and genetic disturbance (Duvall & Wersäll, 1964 Ernstson, 1971).

Following the noise exposure, the degeneration of damaged elements proceeds and reaches its final permanent status only after a longer period of time. In areas of disintegration only the bare basilar membrane remains, covered by a single layer of flat epithelial cells, the spiral vessel and the tectorial membrane Areas of severe distortion end up as a collapsed group of supporting cells with entirely missing hair cells or with only the inner hair cells left. In places where only the inner hair cells remain there is no appreciable retrograde degeneration of the cochlear neurons, as was also observed by Ward & Duvall (1972) and which is in agreement with our earlier finding that 95% of the cochlear neurons are associated with the inner hair cells (Spoendlin, 1972) Scattered degeneration of outer hair cells leaves a normal organ of Corti with just a few missing outer hair cells. The only minor change to remain within an otherwise normal organ are the distorted sensory hairs of the inner hair cells. Swelling of dendrites to the inner hair cells and slight distortion of the outer hair cells are probably reversible to a certain extent (Spoendlin, 1971). Although the structural alterations become more pronounced as the process of degeneration proceeds with postexposure time the extent of damage observed immediately after high intensity exposures does not increase considerably However milder damage after moderate intensity exposures frequently shows up only after a certain time delay in the form of scattered hair cell degeneration.

For easier survey the main types of structural alteration are set out in a diagram which is the exact copy of the original surface preparation of the cochlea (Fig. 1) showing the

missing and disintegrated organ of Corti dif ferent degrees of distortion, and missing hair cells, and which is similar to the cochleogram used in classical surface techniques (Engström et al. 1966)

On the basis of our combined technique of evaluation of ultrastructural damage with reconstruction of the entire cochlea it is possible to compare the extent of structural damage with the intensity of time of exposure. The area of completely missing or disintegrated Corti and the area of distortion were used as structural parameters which can be accurately evaluated and certainly reflect the degree of cochlear damage.

There is a characteristic relation between the extent of immediate structural damage and different exposure times at constant ex posure intensity (Fig. 3 A) At high intensities of 140 dB the curve flattens out to an almost horizontal course after a very short initial steeply raising phase. At lower intensities of 130 dB and less the raising portion of the curve extends over an increasingly longer time before it flattens out. If the time scale is logarithmic the curve becomes a straight line with a small raising angle similar to the TTS which grows linear in the logarithm of time Ward, 1970)

The relation of damage to exposure intensity in dB at constant exposure times, on the other hand, shows a different characteristic of the curve, which above a certain critical intensity level rises with increasing steepness. If however exposure intensity is expressed in a linear way in terms of dyn/cm² the relation appears to become once more a nearly linear function (Fig. 3 B) In order to obtain an equal degree of cochlear damage, the exposure time must be increased exponentially when exposure intensity is decreased.

In conclusion, it is clearly demonstrated that direct mechanical destructions as well as metabolic exhaustion are competing factors in acoustic traumatic damage of the cochlea. Direct mechanical damage is usually irreversible and appears immediately after relatively

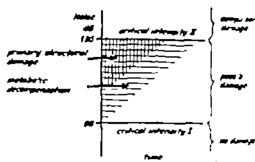


Fig 4 Diagram representing the three intensity zone of sound in respect to its acoustic traumatic effec Up to 90 dB (critical intensity I) no damage is to b expected. Between 90 dB and 140 dB metabolic de compensation occurs increasingly and even primar structural damage might appear to a certain exten In this intensity zone the organ of Corti may or ma not be damaged, at which the exposure time migh be an important factor Above the critical intensity I of 130 dB there is always heavy primary structural irreversible damage of a direct mechanical type eve after very short exposures.

short exposures at high intensities above a certain level whereas metabolically induced damage is partly reversible, occurs after long ex posures with moderate intensities and develops more slowly over a longer period of post-exposure time. Mechanical damage obviously depends on the mechanical resistance of the structure of the organ of Corti and therefore does not show much individual variation. The metabolically induced damage, however ex hibits great differences among the individual animals. Thus in respect of acoustic traumatic effects three zones of intensity can be delineated (Fig. 4) Up to about 90 dB the classical critical intensity level, practically no damage is produced. From 90 to 130 dB permanent acoustic traumatic damage mainly of the metabolic type may occur to a varying extent. Above 130 dB severe irreversible structural damage is unavoidable.

Exposure time and intensity do not seem to be equally responsible for structural damage. At higher intensity levels, exposure intensity is by far more decisive on the extent of damage than is exposure time, except for a short initial period where the time factor appears to be equally important. This initial pe-

riod is very short at high intensity exposures and becomes increasingly longer at lower intensities. Beyond this initial period the amount of damage seems to be mainly defined by the exposure intensity. Thus equal total energy does not seem to produce always the same amount of damage, which is in agreement with recent findings of Ward & Duvall (1972).

RÉSUMÉ

Pour surmonter la difficulté d'obtenir une évaluation globale de toute la cochlée aussi bien qu'un examen au niveau d'ultrastructure nous avons adopté une nouvelle méthode permettant une combinaison entre préparation de surface et de microscopie électronique. Dans les expériments des intensitées de 100 à 140 dB et des temps d'exposition de 30 secondes à une semaine ont été employées. Aux intensités au delà de 125–130 dB un dommage morphologique direct et immédiat est regulièrement observé, dépendant surtout de l'intensité de l'exposition acoustique, tandis qu'aux intensités plus faibles des phénomènes retardés sont prédominants et dépendent surtout de la durée de l'exposition acoustique.

ZUSAMMENFASSUNG

lichtmikroskopischen Übersicht über die ganze …lea und gleichzeitiger ultrastruktureller Unter…ung ausgewählter Abschnitte wurde ein neues Verfahren verwendet, das eine Kombination von Oberflächenpräparation und Elektronenmikroskopie …laubt. Zur Schallexposition wurden Intensitäten …on 100–140 dB mit verschiedener Dauer von 30 Sekunden …s einer Woche verwendet. Die Beziehungen zwischen Ausdehnung oder Art des Schadens zur Dauer und der Intensität der Schallexposition wurden untersucht. … Intensitäten oberhalb 125–130 dB sind direkte …trukturelle, meist irreversible Immediatschaden …ich bei kurzen Expositionszeiten die Regel, wogegen …schwächeren Intensitäten Spätveränderungen vorherrschen, deren Auftreten und Ausmass entscheidend von der Expositionszeit abhängen.

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DISCUSSION

H. Engström. Mr Spoendlin's findings are in agreement with what many other scientists are observing with different kinds of technique. One interesting problem is the occurrence of hearing loss and little modification of the organ of Corti as recently discussed in Chicago. Many scientists are studying the effect of noise and only by a systematic attack with many different approaches can we solve what happens after noise exposure. In Uppsala we work very much along similar lines as Mr Spoendlin and we also use scanning electron microscopy extensively (6 figures shown).

E. Bocca. I should like to know how Mr Spoendlin explains the apparently conflicting evidence resulting from animal observations and from audiometric observation of human subjects exposed to noise.

For extremely high intensities, maximum damage may be a matter of seconds or minutes and cannot possibly be increased by a longer period of exposure. However for critical intensities, total exposure time, or even more so, fractioning of the total exposure time seems to be more important than intensity causing, or preventing noise-induced loss of hearing. Whenever we allow the acoustic cells time enough to rebuild their metabolic reserves, we may even expose

them to short duration high intensity noises with no apparent permanent damage

K H Vosteen. Die systematische Technik von Dr Spoendlin erlaubt mechanische Schäden von Stoffwechselerschöpfung in den Sinneszellen nach akustischem Trauma besser zu unterscheiden. In dieser Beziehung habe ich 3 Fragen: 1) Haben Sie auch längere Zeit (mehr als 2 Wochen) mit geringerer Intensität (90–100 dB) beschallt? 2) Haben Sie auch mit unterbrochenen Tönen oder Geräuschen beschallt? 3) Wie sind die Resultate bei unterschiedlicher Überlebenszeit?

D Hilding. Since we learned of the possibility of using plastic-imbedded tissue for "surface preparations" from Mr Wersäll, we have found the technique to be very useful. My question concerns storage of your beautiful "Loch Ness" displays. Do you have a way to permanently store them? I would suggest replacing glass coverslips and slides with epoxy ones—and mounting in epoxy. This will permit recovery of interesting areas for electron microscopy later

E. Borghesan. Les très belles slides du Mr Spoendlin ont montré la nécrose des groupes bien délimités de cellules sensorielles; je demande s'il y a une prédisposition anatomique et, eventuellement, quelle est.

G Lidén. Would you care to comment further on your experience of the equal energy principle. According to your results would you say that this principle is not generally valid or that it is useful only in certain intensity ranges. Finally have you done any experimental studies on the effect of impact or impulse noise

A C Hilding 1) Did Mr Spoendlin use pure tone or white noise in his experiments? 2) If pure tone did the highly localized lesions produced by lower intensity sound correspond in localization with the pitch of the tone 3) Mr Spoendlin referred to these localized lesions as a result of metabolic charge Does he have an explanation for the sharpness of the localization?

H Spoendlin (Reply) to Mr *Engström* The reason *why we preferred this technique to scanning electron* microscopy is because we consider it very important to be able to survey the entire cochlea in a surface manner and to study every selected part of the same cochlea in light and electron microscopy In scanning electron microscopy you are forced to break open the cochlea, which implies considerable tissue losses and mechanical artefacts. Further evaluation of the same material in light and transmission electron microscopy is limited because of preparation artefacts. It is also our experience that we always find a marked TTS after lower intensity exposures without any significant structural alterations in the cochlea. The first alteration to be observed after low intensity exposures is scattered degeneration of outer hair cells. Sensory hair alterations occur mainly at the inner hair cells but only at somewhat higher exposure intensities.

To Mr *Bocca.* There is not only a difference in noise-induced damage susceptibility between animals and humans but also between different animals. The chinchilla seems, for instance to be much more susceptible than the guinea pig (Ward & Duvall, 1970). The relatively greater importance of exposure intensity for noise-induced cochlear damage was demonstrated for high intensity exposures, where extensive primary damage occurs within a short time after which further increase of exposure time produces only a very small increase of structural damage. At lower exposure intensities the initial rising phase of the damage-exposure-time curve extends over a longer time before it levels out. At this initial rising phase the exposure time seems to have considerable importance and the principle of equal energy might just be valid for this initial phase. It is known that the hearing of "noise workers" who are exposed over years to the same noise does not deteriorate further after a certain number of years.

To Mr *Vosteen.* Low intensity exposures of 110 dB were given for 1 week without any pronounced cochlear damage whereas exposures with interrupted tones in form of speech at peak intensities of 140 dB produced much greater damage than a steady noise exposure at 140 dB So far no combination of noise exposure with hypoxia has been undertaken.

To Mr *Hilding* Our surface preparations are stored in immersion oil where they are always ready for examination and further evaluation.

To Mr *Borghesan.* It is indeed a striking fact that even after very short high intensity exposures a sharply delimited lesion is produced, predominantly *by direct mechanical effects of the sound,* in the lower second or upper basal turn. The reason for this localization might be a greater mechanical susceptibility of the organ of Corti in this region or, even more likely a maximum of volume displacement in this region.

To Mr *Lidén.* This question has been answered in response to Bocca and Vosteen.

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ALKALINE AND ACID PHOSPHATASE ACTIVITY IN POSTAURICULAR SKIN AND CHOLESTEATOMA EPITHELIUM

T Palva, V Raunio and R. Nousiainen

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Abstract. Results are reported on quantitative and electrophoretic analyses of alkaline and acid phosphatase activity in cholesteatoma epithelium and postauricular skin. The activity of these two enzymes was significantly higher in the former than in the latter Only one isoenzyme band with a mobility of α_2-globulins was found for alkaline phosphatase and another with a mobility of α_2-globulin for acid phosphatase in both tissues. The results prove that acid phosphatase plays an important part in keratinization and that the earlier reports of absence of alkaline phosphatase in squamous epithelium were due to the inhibitory effect of cysteine.

Studies on the histochemistry of cholesteatoma epithelium have increased recently since mechanical factors or epithelial immigration alone are insufficient to explain the development of cholesteatomatous disease. Keratinization as such has also become a widely studied subject because the abundant formation of keratin in cholesteatoma is one of its characteristic features (Jarrett et al. 1959).

Release of the hydrolytic enzymes in the granular cell layer determines mainly the type of keratin produced (Jarrett & Spearman 1967). The activity of acid phosphatase is specially noticeable in the granular cell layer and it is the only enzyme that can be demonstrated in great quantities also in the horny layer (Palva et al. 1970) On the other hand, no alkaline phosphatase activity has been found in the keratinizing squamous epithelium though it can be readily demonstrated in the capillary endothelial cells (Wells, 1960 Harris, 1962 Palva et al. 1970)

We have recently shown (Palva et al., 1972) that there is, nevertheless, some alkaline phosphatase activity both in cholesteatoma epithelium and in postauricular and ear canal skin. This activity could be demonstrated by removing the inhibitory effect of cysteine by blocking the active sulphydryl groups with iodoacetic acid. Histochemically however no distinct difference was shown to exist between cholesteatoma epithelium and skin.

We now report on our extended studies using electrophoretic separation of these two enzymes from the cholesteatomatous membrane and skin homogenates and on quantitative determinations of acid and alkaline phosphatase total activity in these two tissues.

MATERIAL AND METHODS

Strips of postauricular skin were removed from 20 patients with cholesteatomatous ear disease undergoing surgery Cholesteatoma epithelium was also removed and both tissue specimens were transported on gauze strips over blocks of ice to the laboratory The tissue specimens, as well as the patient's serum, were stored at −25 C before analyses. For enzyme analysis, the tissue specimens were thawed and homogenization was made in physiological saline with a glass homogenizer at +4 C. An amount of 1-2 ml of saline was used per 1 g of fresh tissue. The homogenate was centrifuged at 40 000 g for 20 min and the clear supernatant was used for quantita

Table I *Phosphatase activity in serum (μmol/min × 1 l)*

20 cases	Phosphatase		Inhibition %	
	Alkaline	Acid	Tartrate	Formaldehyde
Mean	43 4	4 60	16	84
S.D	37 7	3.29	16	20

tive phosphatase determinations and for electrophoresis. Some quantitative measurements were made from a few specimens from the homogenate itself

Electrophoretic separation of isoenzymes was carried out using a Wieme apparatus at +12 C. For alkaline phosphatase analysis 1% agar (Difco special agar) in 0 1 mol/l Veronal buffer pH 9.5 was prepared. For acid phosphatase 1% agar was made in 0 05 mol/l citrate buffer pH 6.2. Electrophoresis was performed for 20 min with a current of 30 mA per slide.

The alkaline phosphatase fractions were stained using the methods of Rawstron (1971) *β-naphthyl phosphate was used as substrate in* 0 1 mol/l carbonate buffer at pH 10 while Fast Blue RR was used as diazo salt. The incubation period was 30 min in room temperature The fractions of acid phosphatase were stained using the method of Smith & hitby (1968)- 10 mg of α-naphthyl phos ate and 10 mg of Fast Blue RR in 10 ml f 0 1 mol/l acetate buffer at pH 5 0 The incubation period was 2 h in room tempera ture.

Quantitative determinations of phosphatase activity were made after the method of King (1965). For acid phosphatase the substrate phenyl phosphate was dissolved in citrate buffer pH 4 9 and for alkaline phosphatase in carbonate buffer at pH 10.0. King's methods were also followed in the inhibition tests for acid phosphatase using tartrate and formaldehyde.

RESULTS

The results of alkaline and acid phosphatase activity tests in serum are shown in Table I together with the inhibition tests for acid phosphatase. Some individual values on the high side appeared but the means are well within the normal range. The inhibition tests show that most of the acid phosphatase is formaldehyde labile (84%) while tartrate has a slight effect only (16%).

Table II shows the corresponding quantitative analyses of the supernatant of the fresh tissue homogenates prepared from cholesteatoma epithelium and of postauricular skin. In a few specimens no alkaline phosphatase activity could be shown but in the majority a small amount of activity was demonstrated. The mean figure for cholesteatoma epithelium was 0.22 μmol/min × g and for postauricular skin 0 07 μmol/min × g. Student's t-test showed this difference to be significant at the $p = 0.02$ level.

Acid phosphatase activity was constantly demonstrated in all analysed homogenates and the mean figures for cholesteatoma and skin were 1.98 and 0.67 μmol/min × g, respectively *Two values in the cholesteatoma group were* markedly elevated (cases 16 and 19). The t-test showed a marginally significant difference between the averages ($p = 0.05$).

Some analyses were also made of the homogenates without centrifugation and, in general, the measured activity increased in varying amounts. This was apparently due to the structure-bound lysozomal enzymes which do not remain in the supernatant after centrifugation.

Table II *Phosphatase activity in fresh tissue homogenates (μmol/min × g)*

20 cases	Phosphatase		Inhibition %	
	Alkaline	Acid	Tartrate	Formaldehyde
Cholesteatoma epithelium (20 cases)				
Mean	0.24	1.98	82	37
S.D	0.27	2.56	22	20
Postauricular skin (20 cases)				
Mean	0.07	0.68	90	35
S D	0.07	0.41	7	20

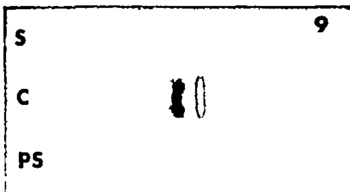


Fig. 1. Electrophoretic analysis for alkaline phosphatase of serum (*S*), cholesteatoma epithelium (*C*) and postauricular skin (*PS*) in case 9. Moderate activity is seen in the area of α_2-globulins for cholesteatoma while very weak bands appear in serum and skin. Control stains without substrate were negative.

The inhibition tests showed similar results in cholesteatoma epithelium and skin homogenates. Both were markedly resistant to the action of formaldehyde (63 and 65% respectively) while tartrate destroyed most of the enzyme (82 and 90% respectively).

In electrophoretic analyses the alkaline phosphatase activity was shown in the form of one rather weak band which migrated anodically from the application point with the mobility of α_2-globulins. The acid phosphatase activity appeared as one single strong band cathodically from the application point, having the mobility of β_1-globulins. The control tests without substrate were negative.

COMMENT

We have earlier demonstrated (Palva et al., 1970) in various enzyme studies that cholesteatoma epithelium has a lively metabolic activity and the present study shows that activity for alkaline and acid phosphatase is significantly higher in cholesteatoma as compared with postauricular skin. Our recent (Palva et al., 1972) histochemical demonstration of alkaline phosphatase activity in these tissues is here corroborated quantitatively and electrophoretically. This enzyme activity which was earlier thought to be absent from cholesteatoma epithelium and skin, is normally inhibited by cysteine, which appears in the sulphydryl groups of the keratinizing epithelium and is missed histochemically if special methods are not resorted to. In respiratory type of epithelium alkaline phosphatase appears both in the epithelial cells and in the ciliae and it can be speculated that inhibition of alkaline phosphatase activity in squamous epithelium is one of the features necessary for keeping the keratinization process going.

Acid phosphatase is one of the most active hydrolyzing enzymes which are released at the level of the granular cell layer. It assists in the breakdown of phospholipids whose energy can be utilized in the keratinization process. In cholesteatoma epithelium, the enzyme activity is marked and continues into the horny layer indicating a strong keratinization process. In normal skin, acid phosphatase activity does not extend into the horny layer and the breakdown of phospholipids may be incomplete. These histochemical observations are corroborated by the present quantitative assessment.

In this study we were particularly looking for such acid phosphatase isoenzyme bands as might be different in cholesteatoma epithelium and skin. However, no such bands appeared and a quantitative difference only was observed.

There appeared to be a clear difference in

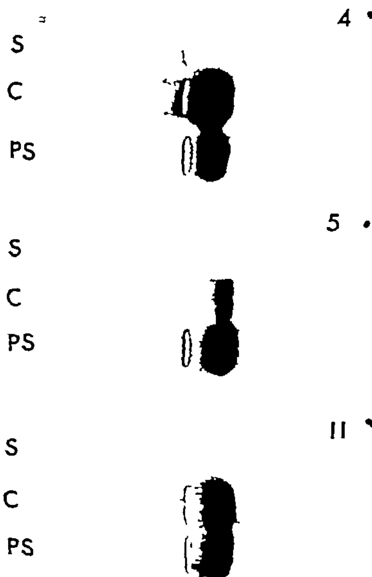


Fig. 2. Electrophoretic analysis for acid phosphatase of serum (*S*), cholesteatoma epithelium (*C*) and postauricular skin (*PS*) of cases 4, 5 and 11. Marked activity appears in the β_1-region with notable individual differences. Control stains without substrate were negative.

the origin of serum and tissue acid phosphatases. In serum they originate mainly from the red cells while in the cholesteatoma epithelium and skin the prostatic-type acid phosphatase dominates.

Cholesteatoma epithelium generally arises from the epidermis at the perforation margin in the form of ingrowing migrating epithelium. In some cases the squamous epithelium retains its normal characteristics of tympanic membrane outer surface, in others it is aggressive, tumour-like cholesteatoma. The latter need by no means be associated with pressure keratinization since the epithelium retains its characteristics even on smooth open surfaces. It is probable that a definite enzymatic change in skin has developed which is responsible for the behaviour of cholesteatoma. There is earlier evidence of increased esterase (Palva et al., 1971) and collagenase (Abramson, 1969) activities in addition to the present evidence of increased phosphatase activity. However the exact process and the many other factors involved remain unknown for the present.

RÉSUMÉ

L'activité de la phosphatase acide et alkaline a été étudiée dans la membrane cholestéatomateuse et dans la peau avec des méthodes histochimiques. Une partie des biopsies a été homogénéifiée et analysée avec des méthodes électrophorétiques. On discute les résultats.

ZUSAMMENFASSUNG

Die Aktivität der sauren und alkalischen Phosphatasen wurden quantitativ und elektrophoretisch aus Homogenaten vom Cholesteatomepithel und postaurikulärer Haut gemessen. Aktivität für beide Enzyme war bedeutend grösser im Cholesteatomepithel. Nur ein Isoenzymband wurde demonstriert mit Mobilität von α_2-Globulin für alkalische und β_1-Globulin für saure Phosphatase. Saure Phosphatase hat einen wichtigen Teil in dem Keratinisationsprozess und die früheren Mitteilungen über den Mangel an alkalischen Phosphatasen sind durch den hemmenden Effekt von Cystein verursacht.

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DISCUSSION

H H Naumann. Das von Herrn Palva festgestellte Vorkommen alkalischer und saurer Phosphatasen in der Cholesteatommatrix erinnert mich sehr an Befunde, die kürzlich Dr J Herrmann, ein Mitarbeiter der Münchner Klinik bei der experimentellen Carcinogenese an Nasenschleimhaut und Gehörgangsband der Ratte finden konnte: In den Bereichen des Epithels, die nach morphologischen Kriterien sich in ein Carcinom umzuwandeln begannen, fand Dr Herrmann sozusagen als Prodromalerscheinung alkalische Phosphatasen in umschriebenen Epithelbezirken. Natürlich ist eine Cholesteatommatrix nicht mit einem Carcinom gleichzusetzen, aber es würde mich interessieren, ob Herr Palva zwischen dem Auftreten der Phosphatasen bei Cholesteatom und bei beginnendem Carcinom theoretisch eine Verbindung sieht.

T Palva (Reply) to Mr *Naumann.* The question of Mr Naumann was much too difficult and complicated for me to offer any clear-cut answer. The only thing I should like to mention is that by the action of phosphatases much energy is being liberated. In skin, and particularly in cholesteatoma epithelium, this energy is needed in the synthesis of keratin molecules. Perhaps in early stages of the development of cancer there is an abnormal protein synthesis and consequently a great need of energy which might be provided by the action of phosphatases.

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ZUR PATHOHISTOLOGIE DES DUCTUS UND SACCUS ENDOLYMPHATICUS

G Zechner

Aus der HNO-Klinik der Universität Graz, Austria

Abstrakt. Ductus und Saccus endolymphaticus sind beim Menschen auf Grund der erhobenen histopathologischen Befunde für die Endolymphphysiologie wichtig. Sowohl die Blockade der Endolymphströmung in den Saccus, als auch Veränderungen an der Pars rugosa des Saccus führen durch Störung der Endolymphaufbereitung zum Endolymphhydrops. Besonders wichtig scheint das Verhältnis epitheliale Oberfläche zu aktivem Gefäßbindegewebe zu sein. Wegsamkeit und Zustand von Ductus und Saccus endolymphaticus sind heute von größerem klinischem Interesse als ehedem der Überleitungsweg von Infektionen.

Cotungo hat 1790 erstmals Ductus und Saccus endolymphaticus in seiner Monographie De aquaeductibus auris humanae internae beschrieben. Erst 1869 folgte Boetchers Darstellung und 1919 Siebenmann dessen Mitteilung us heute mit wenigen Ausnahmen Gültigkeit … Siirala (1942) und Secrétan (1944) haben …ch dann mit pathohistologischen Befunden auseinandergesetzt, einmal beim alten Menschen und zum anderen bei Entzündungsprozessen. Lichtmikroskopische Beobachtungen am normalen Ductus und Saccus endolymphaticus des Menschen stammen weiter von Bast & Anson (1949) Arnvig (1951), zur Pathologie von Zechner & Altmann (1969) Shambaugh (1969) Kaufmann-Ahrenberg et al. (1970)

Sicher sind Ductus und Saccus endolymphaticus kein atavistisches, der Involution anheimfallendes Organsystem. G Portmann hatte schon 1919 und 1922 auf die Bedeutung dieses bei der operativen Schwindelbehandlung verwiesen, Guild (1927) eine Hypothese erstellt, daß beim Hydrops endolymphaticus der Fehler in der Pars rugosa des Saccus liegen müsse. 1938 berichteten Hallpike & Cairns von der perisacculären Fibrose, Anson 1965 von der stiefmütterlichen Behandlung des perisacculären Gefäßbindegewebes. Aktivitätsnachweise, 1956 von Egmond & Brinkmann gefordert, von Ductus und insbesondere Saccus endolymphaticus wurden bislang nur beim Versuchstier geführt Im Ultramikroskop zeigt nach Lundquist et al. (1964) aber auch nach Adlington (1967) das Epithel des Saccus deutlich Merkmale des Flüssigkeitstransportes. Hohe enzymatische und damit Stoffwechselaktivität konnten Ishii et al. (1966), Schätzle & Haubrich (1966) hohen Eiweißstoffwechsel, Koburg et al. (1967) u. a. im Saccus nachweisen Nicht unerwähnt sollten auch die Obliterationsversuche von Kimura (1967), Schuknecht et al. (1962) und Beal (1968) bleiben welche einen Hydrops des Innenohrs erzeugen konnten bei Ausschaltung des Saccus.

Am Menschen sind wir auf Zufallsbeobachtungen angewiesen. Vergleiche zwischen Versuchstier und Mensch sind u. E. nur bedingt möglich, deshalb sind Berichte, ob von post mortem oder Operationspräparaten äußerst wertvoll. Sicher liegen Probleme vor in präparativen Schwierigkeiten. Fäulnis, Fixierung, Entkalkung, aber auch in topographischer Hinsicht bzw der Zuordnung

Herrn Univ Prof Dr E. Navratil zum 70. Geburtstag in Verehrung gewidmet.

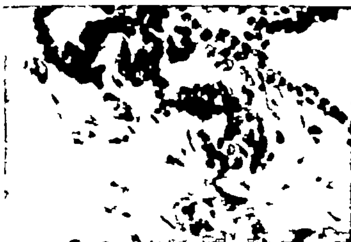


Abb. 1 Pars rugosa, Pollaks Trichrome. Zotten mit Gefäßen im Stiel, lockeres Bindegewebe mit weiten Saftspalten.

bioptisch gewonnener Proben. Wir glauben, daß unsere Mitteilung besonders im Hinblick auf die Beurteilung des gesamten Aquaeductus vestibuli samt Inhalt und wegen der angewendeten Präparation Aussagekraft hat.

MATERIAL UND METHODIK

Unser Material stammt ausschließlich vom Menschen, betrifft alle Altersgruppen wie schon mit Altmann zusammen teilweise 1969 mitgeteilt. Wir haben unsere Untersuchungen fortgesetzt und besonderen Wert auf die Präparation gelegt. Ausgiebige Fixierung frischer Felsenbeine in gepuffertem Formol und schonendste Entkalkung in EDTA bei pH 7,35 scheinen post mortem Artefakte weitgehend auszuschalten. Schnittserien in 15–18 μ Dicke nach Parlodioneinbettung erlauben sehr gute topographische Zuordnung aller Befunde. HE-gefärbte Schnitte dienten vornehmlich diesem Zweck. Pollak's Trichromgemisch als Bindegewebsdarstellung erlaubte gute Beurteilung des Gefäßbindegewebes insbesondere in der Pars rugosa. MPS-Nachweis führten wir mit Hilfe der kombinierten Eisen-PAS-Reaktion nach Mowry. Bezüglich normalanatomischer Befunde verweisen wir auf Bast & Anson (1949) sowie eigene Veröffentlichungen. Das Fehlen einer Basalmembran haben wir 1969 am menschlichen Saccus endolymphaticus mit Hilfe der Versilberung bereits widerlegen können. Neue Erkenntnisse brachten MPS-Darstellungen. Die Dokumentation unserer Befunde legen wir zum großen Teil in Farbdiapositiven dar, welche auch den Wert der präparativen Technik deutlich machen.

PATHOHISTOLOGISCHE BEFUNDE

Im Vestibulum liegen die zwei Wurzeln des Ductus endolymphaticus. Ductus utriculi und sacculi vereinigen sich zum Sinus, welcher wechselnde Größe hat, ablesbar an Faltenbildungen seiner Wand. Am Beginn des Sinus springt vestibulumwärts ein Bindegewebssporn vor, welcher als Bast'sche Klappe bezeichnet wird. Sie ist ähnlich der reinforced area Perlman eine widerstandsfähige Bildung, kann Verziehungen mitmachen, wird aber wie wir beim Endolymphhydrops zeigen konnten, nie aufgebraucht oder an die laterale Wand des Vestibulum gepreßt. So kann das bestehende Sinusostium nur durch überdehnte Teile des utriculus verlegt werden.

Beim Eintritt in den Aquaeductus vestibuli verengt sich der Ductus zur Pars isthmica. Hier ist er mit starken Bindegewebsfasern am Knochen befestigt. Dies ist die Stelle, wo er *offenbar bevorzugt postentzündlich obliteriert*. Wir sahen an der Engstelle Detrituspro-

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Cotungo hat 1790 erstmals Ductus und Saccus endolymphaticus in seiner Monographie De aquaeductibus auris humanae internae beschrieben. Erst 1869 folgte Boetchers Darstellung und 1919 Siebenmann, dessen Mitteilung bis heute mit wenigen Ausnahmen Gültigkeit Surala (1942) und Secrétan (1944) haben dann mit pathohistologischen Befunden auseinandergesetzt, einmal beim alten Menschen und zum anderen bei Entzündungsprozessen. Lichtmikroskopische Beobachtungen am normalen Ductus und Saccus endolymphaticus des Menschen stammen weiter von Bast & Anson (1949) Arnvig (1951) zur Pathologie von Zechner & Altmann (1969) Shambaugh (1969) Kaufmann-Ahrenberg et al. (1970)

Sicher sind Ductus und Saccus endolymphaticus kein atavistisches, der Involution anheimfallendes Organsystem. G Portmann hatte schon 1919 und 1922 auf die Bedeutung dieses bei der operativen Schwindelbehandlung verwiesen Guild (1927) eine Hypothese erstellt, daß beim Hydrops endolymphaticus der Fehler in der Pars rugosa des Saccus liegen müsse 1938 berichteten Hallpike & Cairns von der perisacculären Fibrose, Anson 1965 von der stiefmütterlichen Behandlung des perisacculären Gefäßbindegewebes. Aktivitätsnachweise 1956 von Egmond & Brinkmann gefordert, von Ductus und insbesondere Saccus endolymphaticus wurden bislang nur beim Versuchstier geführt. Im Ultramikroskop zeigt nach Lundquist et al. (1964) aber auch nach Adlington (1967) das Epithel des Saccus deutlich Merkmale des Flüssigkeitstransportes. Hohe enzymatische und damit Stoffwechselaktivität konnten Ishii et al (1966) Schätzle & Haubrich (1966) hohen Eiweißstoffwechsel, Koburg et al. (1967) u. a. im Saccus nachweisen. Nicht unerwähnt sollten auch die Obliterationsversuche von Kimura (1967) Schuknecht et al. (1962) und Beal (1968) bleiben, welche einen Hydrops des Innenohrs erzeugen konnten bei Ausschaltung des Saccus.

Am Menschen sind wir auf Zufallsbeobachtungen angewiesen. Vergleiche zwischen Versuchstier und Mensch sind u. E. nur bedingt möglich, deshalb sind Berichte ob von post mortem oder Operationspräparaten äußerst wertvoll. Sicher liegen Probleme vor in präparativen Schwierigkeiten. Fäulnis, Fixierung Entkalkung, aber auch in topographischer Hinsicht bzw der Zuordnung

Herrn Univ Prof Dr E. Navratil zum 70. Geburtstag in Verehrung gewidmet.



Abb. 3 Pars rugosa. Fe-MPS-PAS Reaktion Basalmembran als Doppelkontur dargestellt zum Teil PAS positiv zum Teil tiefblau (schwarz)

... narbig umgewandelt werden. Sie können ... auch verkleben wodurch lumenfern Zysten entstehen mit eingedicktem Inhalt oder nur Blindsäcke

Auffallend gering sind die Veränderungen an der Pars intraduralis. Das schlitzförmige ... beinhaltet sehr oft eingedickte Massen, inwieweit dies schon krankhaft ist oder ... steht außerhalb unserer Erfahrungen. Bleibt noch die Beobachtung von Makropha... im Lumen des Saccus (Abb 2) einmal reichlich dann wieder spärlich. Die Zellen zeigen hohe Aktivität und scheinen nicht nur corpusculäre Elemente aufzunehmen.

BESPRECHUNG UND WERTUNG DER BEFUNDE

War in der vorantibiotischen Aera das Interesse an Ductus und Saccus endolymphaticu vorwiegend im Oberleitungsweg der Infektion gelegen, so ist durch Portmann und Guild der Einfluß auf die Endolymphphysiologie in den Vordergrund getreten Die heutige gültige Funktionstheorie des Inhalts des Aquaeductus vestibuli umfaßt Resorption und Excretion der Endolymphe Phagozytose und Abwehrmechanismus sowie Endolymphdruckregulation. Unser Bestreben ist es, die erhobenen

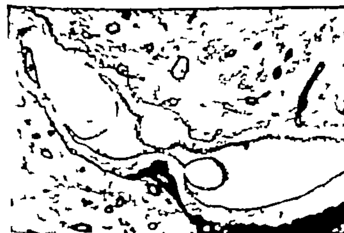


Abb 4 Pars rugosa. HE. Hydropische Zotte mit kleiner Zyste an der lumenabgewandten Wurzel, hydropische Zotte mit metaplastischer Epithelkappe, darunter osteoidartiger Sporn.

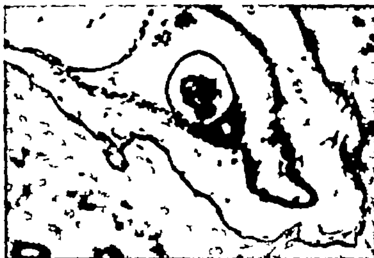


Abb 5 Pars rugosa HE. Zotte mit inkrustiertem Inhalt als Folge von Verklebung.

pathohistologischen Befunde der Organfunktion und deren Störungen zuzuordnen.

1 Ductus und Saccus endolymphaticus haben an der Endolymphcirculation teil. Kommt es zur Unterbrechung entwickelt sich ein Endolymphhydrops. Experimentell haben es Schuknecht und Kimura mit den Obliterationsversuchen gezeigt, wir konnten es bei der bindegewebigen und knöchernen Verödung, aber auch bei Verlegung der Bast'schen Klappe sehen.

2 Aktivster Teil des Labyrinthanhanges ist die Pars rugosa des Saccus. Dies geht schon daraus hervor daß ein Hydrops entsteht, enn die Endolymphe nicht in diesen Teil gengt Hinweise ergeben sich auch aus dem Bau. große epithelisierte Oberfläche, lockeres Gefäßbindegewebe, Zottenbildung und eine durchgehende Basalmembran. Diese ist reich an MPS verschiedener Art und wirkt nach Gussen sowohl als Wasser als auch als aktives Jonenfilter wegen der zahlreichen freien Endgruppen in den MPS. Zellpedikel, Vacuolen, subepitheliale Vesiculation und breite Saftspalten sind Hinweise auf Flüssigkeitstransport.

3 Für eine Funktionsstörung der Pars rugosa scheint es morphologische Belege zu geben: sowohl hyperplastisches Bindegewebe als auch hypoplastisches und Gefäßarmut haben einen Hydrops endolymphaticus zur Folge. Es muß also um die Endolymphaufbereitung gewähr



Abb. 6 Pars rugosa. Zotten und Gefäßbindegewebsatrophie, dystrophischer Kalkherd, daneben ostitische Einsprossung in eine Zotte.

leistet zu sein, ein bestimmtes Verhältnis epithelialer Oberfläche zu aktivem lockerem Gefäßbindegewebe gegeben sein. Dieses Verhältnis wird grob gestört bei allen Formen der Zottenatrophie, Zottenhyalinose, Epithelmeta- und Hyperplasie sowie allen Formen der Bindegewebshyperplasie oder Hypoplasie, wenn sie mit schlechter Vaskularisation einhergeht. Unsere Ansicht bestätigen die bioptischen Befunde von Shambaugh (1969) und Kaufmann-Ahrenberg et al. (1970)

4 Der Druckregelung scheinen Ductus und Saccus nur passiv und in sehr beschränktem Maße zu dienen. Zerdehnungen oder weite geblähte Lumina in der Pars intraduralis konnten wir selbst bei starkem Hydrops nicht sehen. Ob die Bast'sche Klappe eine echte Klappenfunktion erfüllt, ist nicht zu entscheiden.

5 Dem Abwehrmechanismus dienen die immer wieder zu beobachtenden Makrophagen. Diese Zellen liegen im Lumen frei und zeigen deutliche Aktivitätsmerkmale.

RÉSUMÉ

L'état morphologique des structures dans l'aqueduc du vestibule est décrit du point de vue de la fonction du ductus et du saccus endolymphaticus. L image morphologique va de l'altération de la valvule de Bast et de la partie rugeuse du saccus jusqu à l'oblitération osseuse de l'aqueduc.

SUMMARY

Endolymphatic duct and sac are in man, involved in the endolymph physiology as documented by histopathological findings. Blockade of endolymph circulation into the sac leads, by disturbance of endolymph preparation, to an endolymphatic hydrops The relation of epithelial surface to active vascular and connective tissue seems of great importance. Passage and conditions of endolymphatic duct and sac are nowadays of more clinical interest, than in the past as a way of infection.

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DISKUSSION

K H Vosteen. Kennen Sie Fälle mit endolymphatischem Hydrops ohne Veränderungen im Saccus? Und kennen Sie Fälle mit verschlossenen Ductus oder Saccus ohne Hydrops? Ich habe solche Präparate in der Wittmaackschen histologischen Sammlung gesehen.

U Fisch. I would like to ask Mr Zechner if he could say something about the frequency of the changes he has observed. At surgery we found a *total* obliteration of the endolymphatic sac in 20% of the cases and a *partial* obliteration in 30%. We are faced with 50% macroscopically "normal" looking sacs in Menière's disease.

G Zechner (Reply) to Mr *Vosteen.* In agreement with earlier findings we never saw endolymphatic hydrops without alterations of the endolymphatic duct and sac; this is also confirmed by Shambaugh (lack of vascularization). Kaufmann-Ahrenberg, Marovitz and Shambaugh (histologically proven, lack of vascularization) Subotić showed recently in a Mondini-type of hearing loss an aplasia of ductus endolymphaticus and bulging Reissner's membrane as a sign of endolymphatic hydrops.

To Mr *Fisch.* In all our hydrops cases we see various changes microscopically in the vestibular aqueduct. Pure macroscopic findings alone are not so significant for function of the system, although Shambaugh found poor vascularization in operations on the sac.

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DIE HEMMUNG VON LEUKOZYTEN — UND GEWEBSKATHEPSINEN DURCH DEN INHIBITOR DES FLIMMEREPITHELS UND DAS ALPHA 1 ANTITRYPSIN DES SERUMS

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Abstrakt Proteasen aus zerfallenen Leukozyten zerstören körpereigenes Eiweiß, wenn sie nicht durch das $alpha_1$-Antitrypsin des Serums gehemmt werden. Das Flimmerepithel produziert einen niedermolekularen, säurestabilen Proteaseninhibitor (n.m.I.), der eine ausreichend antiproteolytische Konzentration im Nasen- und Bronchialsekret aufrecht erhält. Bei akuten und chronischen Infektionen ist diese Inhibitorkonzentration erniedrigt, bei der Ozaena aufgehoben. Leukozytäre Proteasen zeigen zwei verschiedene Wirkungen: (1) die Destruktion von Basalmembranen und (2) die Aktivierung des Kallikrein-Kinin-Systems, das die Kardinalsymptome der Entzündung auslöst. Die Isolierung von Proteasen aus Eiter ergibt 5 aktive Komponenten, wobei die Fraktion mit der Hauptaktivität durch den n.m.I. voll hemmbar ist. Die Simultan-Immunelektrophorese des Serums bei schweren eitrigen Nebenhöhleninfektionen zeigt hinter dem $alpha_1$-Antitrypsin-peak einen zweiten peak, der den Protease-$alpha_1$-Antitrypsin-Komplex darstellt.

Leukozyten interessieren den Kliniker solange sie als intakte Zellen zu zählen und zu färben sind. Das Interesse sinkt, wenn Leukozyten als Eiter auftreten und erlischt mit dem Zerfall dieser Zellen. Die Erkenntnis, daß Leukozyten auch nach ihrem Zerfall von großer klinischer Bedeutung sind, geht auf die Beobachtung zurück, daß bei noch jugendlichen Patienten mit schweren Lungenemphysemen eine bestimmte elektrophoretische Fraktion im Serum, nämlich die $alpha_1$-Globulin-Fraktion, fehlt (Laurell & Eriksson, 1963). Aus dem Nachweis der Hemmbarkeit aus Leukozyten stammender Proteasen durch das in der $alpha_1$-Fraktion wandernde Globulin, das als $alpha_1$-Antitrypsin bekannt ist, ergab sich die Erklärung für die jugendlichen Emphyseme beim Fehlen der $alpha_1$-Fraktion (Liebermann & Gawad 1971 Ohlson, 1971). In derartigen Fällen werden nämlich die in der Lunge vermehrt anfallenden Leukozytenproteasen nicht ausreichend gehemmt und spalten körpereigene Strukturen wie z. B. Basalmembranen (Frimmer 1971) Ähnliche physiologische Hemmechanismen als Schutz des Organismus vor Autolyse wurden zuerst am Pankreas beobachtet und sind z. B auch von der Blutgerinnung her bekannt. Wir konnten nachweisen, daß ein solcher Vorgang auch im Bereich des Flimmerepithels, also im Bereich der Atemwege von Bedeutung ist. Wir wiesen im Nasen- und Bronchialsekret einen niedermolekularen Proteaseninhibitor nach, der eine Sekretionsleistung des Flimmerepithels darstellt (Hochstrasser et al., 1971 und 1972). Auch dieser Inhibitor hemmt leukozytäre Proteasen, die im Verlauf von Infekten der Atemwege durch Leukozytenemigration — und Zerfall massiert frei werden. In den Sekreten Gesunder liegt dieser Inhibitor in bestimmten Konzentrationen vor Er ist erniedrigt bei Infekten der Atemwege durch verminderte Produktion und durch Bindung an leukozytäre Proteasen. Er fehlt bei schweren eitrigen Infekten und bei der Ozaena (Reichert et al., 1971 Reichert & Hochstrasser 1972).

Der Inhibitor schützt das Flimmerepithel also vor der direkten proteolytischen Einwir

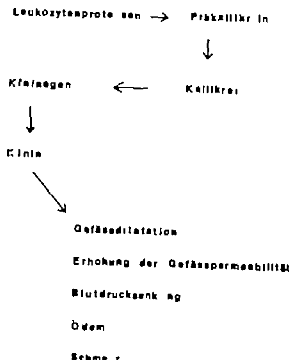
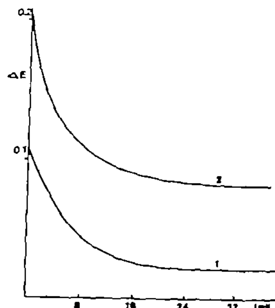


Abb 1



Hemmung on Leuk zytenp otease durch

1 α_1 A titryps n

2 Fl mme ep thel h b to

Abb 2

kung leukozytärer Proteasen. Gleichzeitig wird in der Anwesenheit des Inhibitors noch ein anderer Vorgang unterdrückt, der durch leukozytäre Proteasen ausgelöst werden kann, die Freisetzung von Kininen.

Proteasen aus Leukozyten können wie Entzündungsmediatoren wirken und das Kallikrein-Kininsystem aktivieren. Sie können das ubiquitär vorkommende Präkallikrein durch Proteolyse in aktives Kallikrein umwandeln. Dieses Kallikrein aktiviert seinerseits Kininogen zu (Abb. 1) *Kinin*, einer hochaktiven pharmakologischen Substanz. Kinine lösen die Kardinalsymptome der Entzündung aus. Sie senken den Blutdruck durch Gefäßdilatation erhöhen die Gefäßpermeabilität stören die Mikrozirkulation durch Ödembildung und lösen Schmerz aus. Die Beobachtung, daß Leukozytenproteasen, die sowohl autolytisch wie kininfreisetzend wirken durch den Inhibitor des Flimmerepithels hemmbar sind, und die Absicht diese Beziehung eines Tages klinisch-therapeutisch nutzen zu können, veranlaßte uns, diese Enzyme genauer zu untersuchen.

In unseren ersten Untersuchungen, in denen wir die Hemmbarkeit der Proteasen durch den Inhibitor nachwiesen verwendeten wir Eiter aus Kieferhöhlen der ja ein Gemisch verschiedenster Proteasen darstellt. Wir ließen den Eiter auf natürliche Substrate wie Azokasein und Hämoglobin einwirken, setzten in Parallelansätzen Inhibitor hinzu und stellten fest, daß die proteolytische Gesamtaktivität (Abb. 2) von dem niedermolekularen Inhibitor zu 80% und von dem alpha$_1$-Antitrypsin des Serums zu 60% gehemmt wird. Die nicht hemmbare Restaktivität von 20 bzw 40% führten wir auf Anteile nicht hemmbarer Exopeptidasen zurück. Zur genaueren Differenzierung versuchten wir das Proteasengemisch chromatographisch aufzutrennen und geson-

dert auf ihre Hemmbarkeit zu untersuchen. Durch Chromatographie an DEAE Sephadex gelang eine Auftrennung in 7 Komponenten. Komponente IV und VII enthält keine nennenswerte proteolytische Aktivität. Die aktiven anderen Komponenten wurden an Sephadex G-100 weiterfraktioniert. Dabei wurden letztlich 5 Komponenten gewonnen, die die Hauptaktivität enthalten (Abb 3). Von den verschiedenen Komponenten ist nur die Fraktion V_3, die allerdings die Hauptaktivität enthält, voll hemmbar und zwar sowohl durch unseren Inhibitor wie durch alpha$_1$-Antitrypsin. Dem chemischen Verhalten nach handelt es sich dabei um die Protease, die Basalmembranen abbauen kann.

Nachdem es uns gelungen war aus Leukozyten isolierte Proteasen mit unserem Inhibitor zu hemmen, interessierte es uns zu prüfen, ob auch andere lysosomale Proteasen durch diesen Inhibitor zu hemmen sind. Wir wählten Gewebsproteasen aus der Milz und stellten fest, daß die proteolytische Wirkung solcher Lysosomenpräparate durch unseren Inhibitor nur zu 30% hemmbar ist. Diese Ergebnisse belegen die Hemmspezifität des niedermolekularen Inhibitors und bestätigen damit seine Funktion als Hemmstoff leukozytärer Proteasen im Nasen- und Bronchialsekret.

Nachdem wir das Verhalten unseres Inhibitors in den Sekreten weitgehend geklärt hatten beschäftigten wir uns mit dem Verhalten des alpha$_1$-Antitrypsins, des erwähnten Proteasenhemmstoffs im Serum, der in geringer Konzentration auch in den Sekreten der Atemwege erscheint. Dabei stellten wir in der Immunelektrophorese eitriger Bronchialsekrete fest, daß hinter der alpha$_1$ Fraktion ein zweiter Peak erscheint, den wir als den verzögert wandernden Komplex von alpha$_1$-Antitrypsin mit leukozytären Proteasen auffaßten. In vitro ließ sich dieser Vorgang nachvollziehen, indem wir Serum mit Leukozytenproteasen versetzten und im elektrischen Feld wandern ließen. Mittlerweile gelang es, diesen Komplex u. a. auch in eitrigem Liquor nachzuweisen. Bei schweren lokalen Eiterungen in unserem

Spezifische Aktivität von Leukozytenproteasen gegen Hämoglobin

	∠ E/mg Protein/ h
L I	0 261
L III	0 075
L V$_1$	0 056
L V$_3$	3 44
L VI$_1$	0.071

Abb 3

Fachgebiet, Stirnbeinosteomyelitis, Orbitalphlegmone u. a. beobachteten wir einerseits im Sekret aufgehobener Konzentration an niedermolekularem Inhibitor und andererseits ein deutliches Vorkommen dieses Proteasen-alpha$_1$-Antitrypsinkomplexes im Serum.

Bis jetzt ist nicht geklärt, ob das z. B bei chronisch rezidivierenden Schleimhauterkrankungen nachgewiesene Inhibitordefizit Folge jener Schleimhautaffektionen oder als Ausdruck einer konstitutionellen Produktionsschwäche Ursache jenere erhöhten Erkrankungsrate ist. Angesichts der nachgewiesenen Bedeutung eines ausreichenden Inhibitorspiegels für die Inaktivierung der Leukozytenproteasen erhebt sich darüberhinaus die Frage, ob und auf welche Weise bei Inhibitormangel durch Inhibitorsubstitution ein therapeutischer Effekt erzielt werden kann.

RESUME

Les cathepsins sont des enzymes lysosomales et agissent comme médiateurs d'inflammation. Elle de-

libèrent de l'histamine et de la kinine, fortifient la perméabilité vasculaire, impédient la microcirculation et causent la douleur et l'oedème. Quelques unes d'elles détruisent même les membranes basales. L'inhibiteur de l'épithélium respiratoire, ainsi que l'alpha₁-antitrypsin inhibitent certaines de ces cathepsins. C'est pourquoi ces inhibiteurs influencent le procès d'inflammation.

SUMMARY

Proteases derived from disintegrated leukocytes will split protein structures of the human organism if they are not inhibited by the alpha$_1$-antitrypsin of blood-serum.

The respiratory epithelium produces its own low molecular inhibitor (l.m.i.) to maintain an adequate antiproteolytic concentration in nasal and bronchial mucus. This l.m.i. concentration is reduced during acute and chronic infections and is absent in ozena.

Leukocytic proteases exhibit two different functions: (1) destruction of protein elements such as basal membranes; (2) activation of the kallikrein-kinin-system which leads to the cardinal symptoms of inflammation.

The isolation of proteases from pus reveals 5 active compounds with the main proteolytic activity in a certain fraction, which is completely inhibited by the low inhibitor

The crossed serum immunelectrophoresis of patients with severe paranasal inflammation reveals behind the alpha$_1$-antitrypsin a second peak representing the complex of alpha$_1$-antitrypsin and proteases.

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DISKUSSION

Mr Arslan fragt, ob die interessanten Ergebnisse der Nasenschleimhaut-Biochemie Schule von Prof. Naumann Aufklärungen über die Immunitäts-Mechanismen geben können, die heute eine große Rolle in der Ätiologie der Entzündungen der chronischen Krankheiten der Nasenschleimhaut spielen. Ein bedeutendes Beispiel dieser Pathologie ist die Ozaena, die in der HNO-Klinik der Universität von Padua als autoimmunologische Krankheit studiert worden ist.

R. Reichert (Antwort) zu *Mr Arslan*. Die Anwesenheit des niedermolekularen Proteaseninhibitors im Nasensekret ist unabhängig von immunologischen Vorgängen an der Schleimhaut. Jedenfalls fanden wir in den bisher untersuchten Sekreten von allergischen Rhinitiden weitgehend normale Inhibitorgehalte. Unabhängig von immunologischen Momenten halten wir es für durchaus möglich, daß das Fehlen von Inhibitor im Sekret des Ozaenakranken ätiologische Bedeutung haben kann.

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ZUR ENDOSKOPISCHEN ANATOMIE DER MENSCHLICHEN SIEBBEINMUSCHELN

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Abstrakt. Die Siebbeinmuscheln können bei der Nasenendoskopie eingehend untersucht werden. Damit werden bei ihren vielen anatomischen Variationen, die sich aus der Ethmoidentwicklung ableiten, auch für klinische Belange interessant: die Zelle im Muschelkopf, der Muschelsinus, die Furche oder Incisur im 1. Ethmoturbinale, die Muschelzahl, die Teilmuschelbildung und die Muschelrudimente. Pathologische Veränderungen können nur mit Kenntnis der anatomischen Variationen einwandfrei identifiziert werden; sie reichen von der Taille am freien Muschelrand bei einer kranken Muschelzelle über den Schleimhautprolaps aus dem Muschelsinus mit Furchenbildung am freien Muschelrand bis zur Schleimhaut-Schwellung bzw. Pulsation an der oberen Muschel bei chronischem Hirndruck.

Für die Routine der täglichen rhinologischen Praxis war an den Siebbeinmuscheln bis heute an Besonderheiten lediglich die selten diagnostizierte Concha bullosa von Interesse, während die Vielzahl der anatomischen Varianten, da mit den herkömmlichen Untersuchungsmethoden nicht sichtbar, für die Klinik keine Bedeutung erlangt haben und so praktisch vergessen wurden. Die Nasenendoskopie (Messerklinger 1970) ermöglicht jetzt aber auch einen weiten Einblick in das Ethmoid; damit ist es notwendig, sich mit den anatomischen Variationen des Siebbeinlabyrinths vertraut zu machen, um sie von Erkrankungen differenzieren zu können. Hier sollen nur jene Gebilde besprochen werden, die nach der Definition von Gegenbaur (1880) „von der Wand her entspringende selbständige, von einer einfachen Fortsetzung des Skeletts der Wand gestützte Einragungen" sind; die Bulla ethmoidalis und der Processus uncinatus, die entwicklungsgeschichtlich Zwischenmuscheln sind (Peter 1925; Starck, 1965), seien hier ausgeklammert.

Die untere Siebbeinmuschel bildet in ihrem mittleren und hinteren Drittel durch Einrollen ihres freien Randes nach lateral den Muschelsinus, in den wiederholt die Bulla ethmoidalis ragt. Durch zarte Knochenbrücken wird der Sinus nicht selten in einzelne Nischen unterteilt und kann sich nach vorne blasig ausweiten. Diese Pneumatisation im Muschelkopf, die schon beim Neugeborenen beginnt (Richter 1932) und extrem ausgebildet als Concha bullosa bezeichnet wird, mündet bei kompletter knöcherner Umgrenzung durch ein Ostium an der lateralen Muschelfläche in Höhe des Kieferhöhlenostiums, während sie andernfalls breit in den Muschelsinus übergeht und durch ihn breit mit dem mittleren Nasengang kommuniziert.

Der Muschelkopf scheint dann eine Zelle zu enthalten, wenn er abgerundet ist, während er andernfalls so schmal wie die übrige Muschel ist. Erkrankt eine Muschelzelle, dann schwillt die Schleimhaut über dem Muschelkopf an; am Übergang zum gesunden Muschelteil grenzt sich die Mucosa am freien Rand durch eine typische Taille ab. Dauert die Entzündung längere Zeit, kann am Muschelkopf die Schleimhaut warzig hyperplasieren oder knapp medial von der Kante des Muschelhalses ein solitärer Polyp entspringen,

Herrn Prof. Dr. Robert Stigler zum 95. Geburtstag gewidmet.

der sich im Fornix bis in den Introitus nasi erstrecken kann. Bricht eine kranke Zelle nach vorne durch, so entsteht zuerst am Muschelkopf ein nekrotischer Belag und schließlich kann sich ein solitärer Polyp aus der Zelle stülpen, dessen Stiel auffällig gut zu sehen ist. Nach Abtragen des Polypen findet sich ein nach vorne offener von zarten Knochenwänden umgebener Trichter der mit oedematöspolypöser Schleimhaut ausgekleidet ist. Aus dem Ostium einer kranken Muschelzelle im mittleren Nasengang kann pathologisches Sekret abfließen oder die Mucosa sich halbkugelig vorstülpen.

Auch der Muschelsinus kann vom mittleren Nasengang aus mit Winkeloptiken eingesehen werden. Erkrankt er dann wölbt sich die sehr schwellungsfähige Siebbeinschleimhaut oedematös-entzündlich, hyperplastisch oder polypös verändert in den mittleren Nasengang vor und kann ihn ausfüllen. Am freien Muschelrand entsteht dabei am Übergang zur weniger schwellungsfähigen Mucosa der Muscheloberfläche eine seichte Furche. Lateral der Schwellung ist der mittlere Nasengang frei sondierbar. Ähnliche Erscheinungen, wie z.B. ein überlappender mit hyperplastischer Schleimhaut überzogener Processus uncinatus, kranke Agger nasi-Zellen oder ein Prolaps einer vorderen unteren Fontanelle sind dadurch leicht vom kranken Muschelsinus zu differenzieren (Abb. 1. 10–20 bei Messerklinger (3)).

In den meisten Fällen kann man mit dem Endoskop über den Recessus sphenoethmoidalis, manchmal auch zwischen Septum und mittlerer Muschel tief in das Siebbein eindringen und die weiteren Muscheln und Nasengänge mit ihren verschiedenen Varianten nebst Furchen- und Spaltbildung untersuchen. Die Vielfalt dieser Bildungen ist nur aus der Kenntnis der Ethmoidentwicklung zu verstehen. Es bestehen zwar in dieser Frage noch verschiedene Meinungen, die vor allem dann hervortreten, wenn man z.B. die Artikel von Hochstetter (1944), Killian (1896), Grünwald (1917). Peter (1913) und Richter (1932) nebeneinander stellt, das für hier Wichtige dürfte aber im Wesentlichen geklärt sein.

Durch Eindringen von Epithelfurchen oder Rinnen und Gewebsvermehrung der so herausgeschnittenen Wülste werden die Ethmoidmuscheln gebildet, wobei die Epithelfurchen primär gestaltend sind (Grünwald, 1917). Von den Hauptwülsten – Hauptmuscheln werden nach Killian 5–6, nach Peter höchstens 3, Richter 3 und Grünwald je nach Individuum 3 oder 2 angelegt, wobei in der Reife der größere Teil der 2-wulstigen durch Reduktion aus 3-wulstigen entsteht. 23 % von entwickelten plus 10 % rudimentären obersten Muscheln beim Erwachsenen stehen 48 % im 8.–10. Foetalmonat angelegten gegenüber (Grünwald). Peter will hingegen in der Reife nur 2 Hauptmuscheln ausgebildet sehen und klassifiziert eine oberste Muschel als Teilmuschel der oberen. Dem hält Richter entgegen, daß in der obersten Muschel später als in der oberen die Knochenbildung einsetzt und eine Concha suprema wiederholt größer ist als eine obere Muschel. Vor allem auf dem 1. Ethmoturbinale kommen Nebenfurchen vor, die eine mehr oder weniger ausgeprägte Teilwulstbildung bedingen können. Im 5. Foetalmonat fand sie Grünwald in 59 %, beim Erwachsenen in 6 %. In seltenen Fällen können die Furchen und Spalten die hintere oder vordere Grenze der Muschel überschreiten.

Endoskopisch konnte ich am Menschen beobachten, meist ist nur eine obere Muschel vorhanden, die frei endet (Abb. 10 bei Messerklinger (2)) oder auch in die Rückwand des Recessus sphenoethmoidalis auslaufen kann; ihr vorderes Ende kann schlank sein oder auch einen Lobulus aufweisen. Im darunterliegenden Nasengang kann sich mitunter eine schmale Leiste finden, die nicht mehr das Niveau der Muschel erreicht und auch nicht mehr die ganze Länge des Meatus einnehmen muß. Sie ist eine rudimentäre 2. Siebbeinmuschel, während das anfangs als obere Muschel imponierende Gebilde eine Concha suprema ist (Abb. 11 bei Messerklinger (2)). Diese Bildungen lassen sich zwanglos in die

Beobachtungen Zuckerkandls (1893) oder die verschiedenen Typen Grünwalds einreihen. Eine 2. und 3. Siebbeinmuschel kann aber auch voll ausgebildet sein und die 3. sogar ein Tuberculum ethmoidale posticum (Zuckerkandl) aufweisen, das in den obersten Nasengang mündet (Abb. 1). Auch ein 4. Ethmoturbinale kann in seltenen Fällen vorkommen (Abb. 2), ob es ein Teilwulst oder eine Hauptmuschel ist, läßt sich aus der Beobachtung allein nicht entscheiden.

Furchen verschiedener Länge finden sich mit Vorliebe an der medialen Fläche des 1. Ethmoturbinale, knapp über dem freien Rand und mit ihm parallel laufend (Abb. 2 bei Messerklinger (3)). Schneiden sie ausnahmsweise tiefer ein, so können sie eine mehr oder weniger ausgeprägte Teilwulstbildung bedingen, diese Teilmuscheln können ein gemeinsames Ende haben, oder, was selten ist, ihr Ende durch eine Incisur geteilt und damit schwalbenschwanzartig sein (Abb. 3 bei Messerklinger (3)). Schwieriger wird die Entscheidung, wenn knapp hinter dem Kopf der 1. Siebbeinmuschel und manchmal auch noch unter ihrem Hals eine Muschel durch eine tiefe Furche abgetrennt ist (Abb. 3), die fallweise im vorderen Abschnitt bis an den freien Rand der 1. Siebbeinmuschel herabreichen (Abb. 4) und damit große Ähnlichkeit mit dem 2. Ethmoturbinale des Schimpansen haben kann (Zuckerkandl). Der freie Rand eines solchen Gebildes verläuft nach rückwärts aufwärts und endet, wiederholt in die Rückwand des Recessus sphenoethmoidalis übergehend, in derselben Höhe wie eine 2. Siebbeinmuschel, gerade der letztere Grund könnte dafür sprechen, daß es sich bei dieser Bildung doch um eine 2. Siebbeinmuschel handelt und nicht um eine Teilmuschel des 1. Ethmoturbinale. Ebenfalls selten kann zwischen dem Hals der 1. Siebbeinmuschel und dem Septum der Kopf eines Ethmoturbinale vorragen und in der Frontalebene bis oder über den Kopf der mittleren Muschel reichen (Abb. 5).

Finden die bisherigen Beobachtungen noch mit den vielfältigen Möglichkeiten aus der Siebbeinentwicklung eine Erklärung, so komplizieren Doppelungen des Kopfes der mittleren Muschel, und zwar Doppelungen zwischen Septum und Muschelkopf und nicht wie aus der Pathologie bekannt im mittleren Nasengang, das Bild außerordentlich. Ich konnte bisher zwei solche Fälle beobachten: im ersten war die mediale Doppelung durch eine Furche vom Muschelkopf getrennt, nach dem Tastbefund fehlte ihr eine knöcherne Grundlage und als man mit dem Endoskop in die Furche eindrang, erschien dahinter eine Muschel, die mit der mittleren gemeinsam endete. Im zweiten Fall fand sich ein zu großer weicher Muschelkopf, an dessen medialer Fläche eine breite Furche begann (Abb. 6, 7), die bis knapp vor das hintere Ende die Concha media in zwei Teilmuscheln trennte (Abb. 8), ungefähr am Ende des Muschelkopfes strahlte eine zweite frontal verlaufende Furche in die erstgenannte sagittale ein und setzte so den fleischigen Kopf deutlich von der Muschel ab (Abb. 9). In der anderen Nasenhälfte desselben Individuums war der Kopf der mittleren Muschel ebenfalls größer und hatte an der medialen Fläche ein tiefes Grübchen (Abb. 10). Diese Bildung des Muschelkopfes aus der Siebbeinentwicklung zu erklären ist unmöglich. Richter & Spuler kamen bei ihren entwicklungsgeschichtlichen und anatomischen Studien zur Überzeugung, daß ein Rest des Nasoturbinale im nach abwärts gerichteten vorderen Ende der mittleren Muschel enthalten ist. Dies könnte auch die zwei angeführten Beobachtungen erklären und wird auch dadurch wahrscheinlich, als ich bei einem meiner Fälle an der lateralen Fläche einer mittleren Muschel am Ende des Muschelkopfes eine fast vertikal verlaufende Furche beobachten konnte (Abb. 11), die ebenfalls aus der Siebbeinentwicklung nicht erklärbar ist.

Furchen am freien Rand des 2. oder 3. Ethmoturbinale sind bisher nicht beobachtet worden. Am freien Rand einer oberen Muschel konnte ich eine Furche beobachten, die beidseits von etwas verdickter oder gestauter

Schleimhaut begrenzt war und eine Ähnlichkeit mit der Furche am freien Muschelrand bei einer Erkrankung des Muschelsinus hatte (Abb 12) Es fehlte jeder Anhalt für eine entzündliche Genese Da die Schwellung im hinteren oberen Recessus sphenoethmoidalis zunahm und den Blick zum Keilbeinostium verlegte, wurde der 56 Jahre alte Kranke eingehend untersucht und dabei ein chronischer Hirndruck mit Stauungspapille als Folge eines großen parasagittalen Meningeoms gefunden. Drei Monate nach der Operation war die Furche noch zu sehen, die Schleimhaut aber unauffällig und der Blick zum Ostium sphenoidale frei. Die Schleimhautschwellung dürfte somit die Folge des Hirndrucks gewesen sein. Beim Tier sind ja innige Verbindungen zwischen dem Subarachnoidalraum und dem Lymphgefäßnetz der Nasenschleimhaut bekannt, die nach den Untersuchungen von Hoffmann & Thiel (1956) wahrscheinlich über die Perineuralscheiden des N olfactorius und die Gewebsspalten in die Nasenlymphgefäße gehen. Beim Menschen konnte eine solche Verbindung bisher nur im 1 Lebensjahr nachgewiesen werden (André, 1905 Zwillinger 1914) während sie beim Erwachsenen ganz oder großteils obliteriert sein soll (Grünwald) Daß die oben angeführte Beobachtung kein Zufall ist, zeigte mir die Untersuchung eines weiteren chronischen Hirndrucks bei einem 5 Jahre alten Kind, das an einem Kleinhirntumor erkrankt war· die Mucosa war zwar nicht wesentlich gestaut und auch der Blick zum Ostium sphenoidale war frei, die Reflexe auf der Schleimhaut der oberen Muschel und des hinteren oberen Septums zeigten aber eine deutliche Pulsation.

Die Folgerung aus diesen Beobachtungen ist, daß nur die Kenntnis der vielen aus der Siebbeinentwicklung möglichen anatomischen Variationen es ermöglicht endoskopisch pathologische Veränderungen an den Ethmoturbinalien zu erkennen und einwandfrei zu identifizieren.

RÉSUMÉ

Il est possible d examiner à fond les cornets de l'ethmoïde grâce à l'endoscopie endonasale. Ainsi ses multiples variations anatomiques dérivant du développement de l'ethmoïde sont également intéressantes pour le domaine clinique· la cellule dans la tête du cornet, le sinus ethmoïdal, le sillon ou l'incision du premier cornet de l'ethmoïde, le nombre de cellules ethmoïdales, la formation partielle des cellules et les ébauches de l'ethmoïde. Les malformations pathologiques sont entièrement identifiables seulement quand on connaît les variations anatomiques; elles vont de l'entaille au bord libre de l'ethmoïde dans le cas d une cellule ethmoïdale malade en passant par le prolapsus de la muqueuse provenant du sinus

Abb 1 Linke Nase· Ethmoturbinale II und III mit Tuberculum ethmoidale posticum und Mündung einer Siebbeinzelle in den obersten Nasengang. *Abkürzungen* Agn – Agger nasi ET I II, III – Ethmoturbinale ET I, II, II F – Foveola I – Incisur S – Septum Tep – Tuberculum ethmoidale posticum.

Abb 2 Rechte Nase. Ethmoturbinale II, III und IV

Abb. 3 Linke Nase. von der medialen Fläche des Ethmoturbinale I entspringende Concha, die wie ein Ethmoturbinale II endet

Abb. 4 Linke Nase von der medialen Fläche des Ethmoturbinale I entspringende Concha, die nach caudal bis an den freien Rand der mittleren Muschel reicht und rückwärts wie ein Ethmoturbinale II endet.

Abb. 5 Linke Nase· knöcherne Hyperplasie des Kopfes von Ethmoturbinale II die in der Frontalebene weit den Hals von Ethmoturbinale I nach vorne überragt.

Abb. 6 Linke Nase: lappige Hyperplasie des Kopfes von Ethmoturbinale I mit halbkreisartiger Furchenbildung an der medialen Seite des Kopfes, die bis knapp vor das Muschelende reicht.

Abb. 7 Wie Abbildung 6: Blick in die Furche· durch eine zusätzliche frontale untere Incisur ist der hyperplastische Muschelkopf nach vorne deutlich abgesetzt.

Abb. 8. Wie Abbildung 6. sagittale Incisur die bis knapp vor das hintere Ende die Concha media in 2 Teilmuscheln trennt.

Abb 9 Wie Abbildung 6. am Ende des Muschelkopfes strahlt eine frontal verlaufende Furche in die sagittale ein und setzt so den fleischigen Muschelkopf deutlich von der Muschel ab.

Abb. 10 Rechte Seite von Abbildung 6. vergrößerter Kopf von Ethmoturbinale I mit Grübchen an der medialen Fläche.

Abb 11 Rechte Nase: Incisur an der lateralen Fläche eines Ethmoturbinale I am Ende des Muschelkopfes.

Abb 12. Linke Nase· Ethmoturbinale II mit zarter Furchenbildung am freien Rand, wahrscheinlich als Folge eines chronischen Hirndrucks



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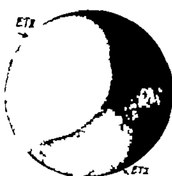
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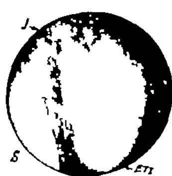
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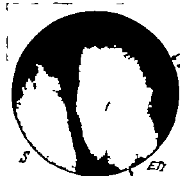
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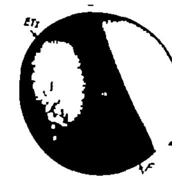
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ethmoidal avec formations de sillons au bord libre de l'ethmoide. Jusqu'à la tuméfaction, voire la pulsation de la muqueuse à l'ethmoide supérieur accompagné de pression cérébrale chronique

SUMMARY

The ethmoturbinals can be examined with precision by nasal endoscopy The numerous anatomical variations deriving from the ethmoidal development are therefore of clinical importance: the cell in the concha's head, the concha sinus, the rim or incision of the first ethmoid concha, the number of conchae, the partial development and the concha rudiments. Pathological changes can be identified only with profound knowledge of the anatomical variations. They include the waist at the free end of the concha in a sick cell of a concha, the mucosal prolapse out of a concha sinus with rim formation at the free end of the concha mucous swelling or pulsation in the superior concha with chronic intracranial pressure.

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EFFECT OF TESTING TECHNIQUE ON NASAL PRESSURE VARIATION

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Abstract The effect on nasal pressure change of breathing through a mask was studied in supine position by anterior rhinomanometry. Irrespective of the effect of shrinking drugs or the anatomical or functional health of the nose, a significant increase was observed in both inspiratory pressure fall and expiratory pressure rise when testees were breathing through a mask. In a majority of cases, an increase in pressure change was observed leading to a different clinical result. Intensive studies of all technical details is recommended before a testing technique is adapted.

Of the available tests of nasal respiratory function, rhinomanometry has gained increasing clinical attention and acceptance during recent years. The techniques applied for this purpose are numerous and several parameters can be measured. The effect on pressure of the nose, a fall during inspiration and a rise during expiration, is easiest to record and accordingly is the parameter most often determined. On the other hand, a great variability in results of pressure rhinomanometry, due for instance to the nasal cycle, has aroused considerable criticism against this test method (Williams et al., 1970).

Even the effect of introducing the testing device into the nose has been claimed to be significant and a source of error (Rundcrantz, 1970). In the present study, the effect of placing a mask on the face of the testee has been analysed, as, according to our preliminary observations, this could be a source of variability in certain individual tests.

In this paper, only the effects on nasal pressure of breathing through the mask are considered. An anterior rhinomanometry technique was used, due to the fact that in all attempts with a posterior recording the accumulation of secretion into the mouth made the test unreliable, because of several interruptions during the relatively long testing time.

The following technique was applied. A catheter, a standard No. 10 oxygen catheter with a sponge tip, was fixed airtightly to the contralateral nostril. The tip of the catheter was made airtight with a mixture of paraffin oil and vaseline, and fixation was completed with tapes. In this way an optimally stable fixation of the pressure detector was gained. This is proved by the few statistically significant changes recorded between the first and last testing period. The catheter was connected to an electromanometer calibrated for rhinomanometry. The testee remained supine during the whole test period and was asked to breathe quietly.

Recordings were made in several periods. In the first phase, a primary recording was taken when the testee appeared to have got used to bearing the catheter. Each recording period lasted for no less than 6 consecutive breaths, usually from 8 to 12. Half a minute later, a secondary period was recorded and during continuous recording a mask was placed on the testee's face. This began the second phase with an immediate recording period of breathing through the mask. The mask was a simple diver's mask designed for a flow test so that it did not distort the external nose

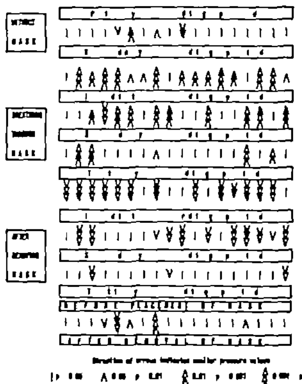


Fig 1 Mean inspiratory pressure changes between consecutive recording periods and in the beginning and at the end of the test Vertical lines represent one continuous test.

and yet fitted airtightly on the face (Kortekangas, 1971) Two additional periods were recorded while breathing through the mask, e secondary recording period after a half inute pause and the tertiary recording period after a 1 minute pause. Recording continued when the mask was lifted from the face and this moment initiated the third phase with an immediate recording period after removing the mask. Again two control recording periods were taken the secondary recording period after a half minute pause and the tertiary recording period after a 1 minute pause.

The mean respiratory pressure falls in relation to ambient pressure of each breath of the above periods were statistically compared applying Student s *t*-test. The results from 18 testees, subjects with pathological and normal noses, are given together due to the fact that no differences in reaction could be traced as related to the nasal state

RESULTS AND DISCUSSION

In Fig. 1 mean inspiratory pressure changes in this trial are given. There are significant changes in the mean inspiratory pressure fall in four cases between the primary and secondary period without mask at the beginning of the test with the testee breathing through one nostril, an increase in two cases and a decrease in two Considering the frequency of variation in nasal pressure changes this is an unexpectedly low incidence and is certainly due to the fact that most of these tests were made at a time when the effect of an earlier shrinkage of the mucosa still persisted.

When mean inspiratory pressure changes in the beginning and at the end of the whole test were compared, a significant change was seen in five cases, a pressure fall in two and a pressure rise in three. This result constitutes the main proof of the validity of this test, which revealed a pressure rise when the testee was breathing through a mask and pressure fall when the mask was withdrawn. This change could appear immediately during the first breath or a few moments later The moment of appearance of this reaction seems to be individual, but very often either the immediate or the delayed type was characteristic both under the mask in the rise and after its withdrawal in the fall.

As the results of consecutive expiratory changes between all the periods of the test were very similar to those of the inspiratory test, the expiratory results are not given in detail.

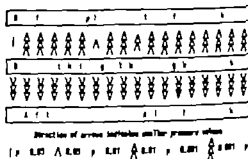


Fig 2. Mean inspiratory pressure changes.

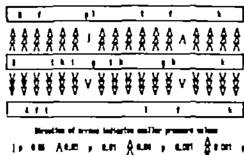


Fig. 3. Mean expiratory pressure changes.

Figure 1 records only the significance of changes between adjacent recording periods and a slow reaction may thus be hidden. For this reason, a comparison of mean pressure fall over three phases, before placement of the mask, during breathing through the mask and after its withdrawal, are given in Fig. 2. The corresponding pressure rises during expiration are given in Fig. 3. This result shows that breathing through a mask in supine position causes a significant increase in both inspiratory and expiratory nasal pressure changes.

When the change is considered in terms of normal nasal respiratory pressure change (≤15 mm/H_2O), elevated nasal pressure change (16–30 mm/H_2O) or highly elevated pressure change (>31 mm/H_2O) the following result was obtained. In 6 testees, the pressure remained normal during the whole test. In 10 testees, nasal pressure change was normal without the mask but became elevated when the testee was breathing through the mask. In one testee, the mean pressure rise reached 58 mm/H_2O. In one testee, pressure remained elevated during the whole test.

This observation cannot be ignored in the evaluation of rhinomanometric pressure tests. Before any specific testing technique can be recommended for general use, intensive studies should be made on each detail of the procedure involved.

RÉSUMÉ

On a utilisé la technique du masque dans la rhinomanométrie antérieure. Les changements dans les variations de la pression nasale sont analysés du point de vue de la respiration libre et la respiration par un masque.

ZUSAMMENFASSUNG

Die Wirkung der Maskenatmung am rhinomanometrischen Drucktest bei liegenden Versuchspersonen ist untersucht worden. Eine anteriore Rhinomanometrie mit fixiertem Druckkatheter erwies sich stabil genug für wechselweise Registrierung ohne und durch die Maske. Ein statistisch signifikantes Steigen sowohl der inspiratorischen als der exspiratorischen Druckveränderungen konnte man unter Maskenatmung sehen, ohne dass Personen mit pathologischen Nasenveränderungen ein verschiedenes Verhalten von Normalpersonen aufwiesen. In der Mehrzahl der Fälle war diese Veränderung bedeutend genug, sodass die Resultate der Rhinomanometrie klinisch als pathologisch durch die Maske und normal ohne sie zu beobachten war. Ein sorgfältiges Studieren aller Einzelheiten und deren Wirkung an den Resultaten ist notwendig bevor eine rhinomanometrische Methode empfohlen werden kann.

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ON THE ORIGIN OF POSITIONAL ALCOHOL NYSTAGMUS

W J Oosterveld

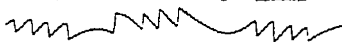
From the Department of Otolaryngology University of Amsterdam, Amsterdam, The Netherlands

Abstract. The vestibular system plays an important role in the origin of positional alcohol nystagmus (P.A.N). An investigation was performed on the effect of artificial lesions in the peripheral vestibular organs of rabbits upon P.A.N. In rabbits in which the otoliths were eliminated on both sides, a P.A.N could not be provoked. If on one side the labyrinth was totally destroyed, a P.A.N could still be elicited, but if in the only intact labyrinth the utricular nerve was also transected a P.A.N could no longer be elicited. That the otoliths are responsible for the P.A.N also finds support in the fact that increased g forces effect a P.A.N in rabbits as well as in man.

Positional alcohol nystagmus following administration of alcohol to animals was demonstrated for the first time in 1842 (Flourens). Bárány (1911) and Bárány & Rothfeld (1913) were the first to perform experimental studies order to evaluate the effect of alcohol upon the vestibular system.

Since positional alcohol nystagmus has been described in experimental studies in animals and man by various authors (Goldberg, 1941 1943 1966 Plenkers, 1943) In 1956 nystagmographic studies were performed for the first time (Aschan et al., 1956, 1965 Aschan & Bergstedt 1957) Positional alcohol nystagmus appears in two phases (Aschan, 1958 Walter 1954) The first phase (PAN I) appears 20–30 minutes after the intake of alcohol and shows a nystagmus with the fast component beating in the direction of the side position i.e. in left-side position to the left and in right side position to the right. The first phase lasts about 3 hours. 1 $^1/_2$–2 hours later the second phase (PAN II) appears when the subject is in lateral position but the direction of this nystagmus is opposite to the direction of PAN I. PAN II goes on up to 10 hours after the intake of alcohol. PAN can only be elicited if there is an intact vestibular apparatus, after bilateral labyrinthine destruction PAN can no longer be provoked, neither in rabbits (De Kleyn & Versteegh, 1930) nor in humans (Fregly & Graybiel, 1968 Harris et al. 1962) De Kleyn & Versteegh (1930) described that extirpation of the saccule did not have any effect on the appearance of PAN (1930) after labyrinthectomy on one side, alcohol nystagmus could still be provoked but in the side position opposite to the operated ear only Nito et al. (1964) found in experiments in cats that PAN does not occur following the inactivation of all six semicircular canals. This indicates that the semicircular canals are necessary to elicit PAN Money et al. (1965) inactivated both the horizontal semicircular canals in cats, after which a horizontal alcohol nystagmus could no longer be elicited in any position, but the vertical and rotatory components of the nystagmus were still present. These authors state that positional alcohol nystagmus is initiated by the action of gravity on receptors of the semicircular canals. However the functional control tests in their experiments were not very accurate.

Hill et al. (1972) found no consistent effects of alcohol on either the vertical nystagmus or the vertigo produced by coriolis stimulation.



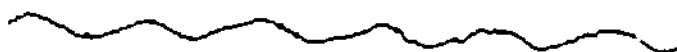








Fig 1 Normal rabbit. *A* No preponderance. *B* Equal sinusoidal eye-movements in both side positions. *C* Equal P.A.N in both side positions.

Decrease in turning sensations and in nystagmic responses to angular acceleration were found and most evident during the first hour or two after drinking. This last finding points to an effect of alcohol on the processing of information from the semicircular canals. The review of the literature shows that the investigators do not agree on the origin of positional alcohol nystagmus. In order to gain more insight on the origin, we investigated the alcohol nystagmus in rabbits which had artificial lesions of the peripheral vestibular apparatus.

These rabbits were normal laboratory animals, all in good health, free from spontaneous or positional nystagmus. They had no directional preponderance in the torsion-swing test, equal reactions in the parellel-swing test, this means sinusoidal eye movements in left and right-side position when swinging sideways, as well as in the direction of the longitudinal body axis, and an equal irritability of the labyrinths in the caloric test.

Six groups of 10 rabbits each were subjected three times to experiments in which alcohol nystagmus was provoked by means of intraperitoneal administration of ethyl alcohol. The eye movements in the horizontal plane were recorded nystagmographically The recordings with the animals were made in total darkness. The rabbits collected in one group all had a specific lesion of the vestibular apparatus.

Group I consisted of normal rabbits. Group II consisted of rabbits which were labyrinthectomized on one side in group III the rabbits were labyrinthectomized on both sides. The utricular nerve was transected on one side in the rabbits of group IV and both the utricular nerves were transected in the rabbits of group V In the last group VI rabbits were labyrinthectomized on one side and utriclectomized on the other side.

Labyrinthectomies were performed in the way described by Versteegh (1927). The surgery on the utricular nerve was done by the same approach. Surgery of two ears was always performed in two steps, one step for each ear with an interval of 4 weeks. The results of the surgery were functionally controlled. the labyrinthectomies by the non irritability to caloric testing and a directional

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ON THE ORIGIN OF POSITIONAL ALCOHOL NYSTAGMUS

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Abstract The vestibular system plays an important role in the origin of positional alcohol nystagmus (P.A.N.). An investigation was performed on the effect of artificial lesions in the peripheral vestibular organs of rabbits upon P.A.N In rabbits in which the otoliths were eliminated on both sides, a P.A.N could not be provoked. If on one side the labyrinth was totally destroyed, a P.A.N could still be elicited but if in the only intact labyrinth the utricular nerve was also transected, a P.A.N could no longer be elicited. That the otoliths are responsible for the P.A.N also finds support in the fact that increased g forces effect a P.A.N in rabbits as well as in man.

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A. TORSION SWING TEST



LEFT SIDE POSITION



B. PARALLEL SWING TEST

RIGHT SIDE POSITION



LEFT SIDE POSITION



C. P A N

RIGHT SIDE POSITION



Fig. 4 Rabbit in which both the utricular nerves are cut through. *A* No directional preponderance. *B* No response. *C* No response.

ml ethanol 96% per kg bodyweight was administered intravenously in a 20% diluted solution with normal saline. In most cases PAN was noticed to appear within 10 minutes after the administration of alcohol. In some experiments higher g-values were applied. This was performed in the way described in earlier publications (Oosterveld & van der Laarse, 1969 Oosterveld, 1970).

RESULTS

Group I

The normal rabbits showed a PAN in both side positions. In 6 out of 10 rabbits there was a small difference in frequency between the nystagmus to the right and to the left, but always less than 10% (Fig. 1).

Group II

In the rabbits with the unilaterally destroyed labyrinth the alcohol nystagmus was present when the rabbits were in the side position on the intact labyrinth. The other side position provoked in 6 rabbits a very slight nystagmus but in the remaining rabbits no nystagmus at all (Fig. 2)

Group III

None of the rabbits with the bilaterally destroyed labyrinths presented a PAN after the application of alcohol. Even with doubled dosage no PAN could be provoked, nor when the rabbits were subjected to higher g-values, up to 3-g.

Group IV

In the rabbits with the unilateral utriclectomy a clear PAN could be provoked when the animals were put in the side position opposite to the operated ear. Only 2 rabbits out of 10 showed some nystagmus beats when put in the side position on the operated side (Fig. 3).

Group V

None of the bilaterally utriclectomized rabbits of group V showed any nystagmus after the alcohol administration. No vertical or rotatory movements were noted. The rabbits of this group were subjected to higher g-values, up to 3-g, but this condition had no effect on the findings. Even an increase of alcohol dose with a factor 2 up to 4 cc/kg did not provoke a nystagmus (Fig. 4).

A TORSION SWING TEST

LEFT SIDE POSITION

B PARALLEL SWING TEST

RIGHT SIDE POSITION

LEFT SIDE POSITION

C P.A.N

RIGHT SIDE POSITION

Fig 5 Rabbit in which the labyrinth on the right side is destroyed and the utricular nerve on the left side is transected. *A* Nystagmus preponderance for a nystagmus to the left. *B* No response. *C* No response.

Group VI

The rabbits of the last group had one labyrinthectomized ear and one sectioned utricular nerve on the other side. None of these animals showed a PAN nor when the alcohol dosage had been doubled. Here neither vertical nor rotatory eye-movements were noted (Fig. 5) Table I shows the combined results of all the experiments.

Table I

	Responses on vestibular tests: Rotation test response			Linear acceleration test response			Caloric test response			P.A.N: Present		P.A.N: Absent
[illegible]	No nystagmus preponderance	Nystagmus preponderance	No response	No preponderance effect in side positions	Preponderance effect in side positions	No response	Both sides	One side	No response	Equal effect in [illegible]	No equal effect in [illegible]	
Normal	•			•			•			•		
Labyrinthectomized on one side		•			•			•				
Labyrinthectomized on both sides			•			•			•			
Utriculectomized on one side	•				•		•				•	
Utriculectomized on both sides	•					•	•					•
Utriculectomized on one side and labyrinthectomized on the other side		•				•		•				

CONCLUSION

Rothfeld (1913) pointed to the regularity of the phenomenon of positional alcohol nystagmus observed in lateral positions of the head

The results of our experiments point to the conclusion that the utricle is an essential organ for the genesis of positional alcohol nystagmus.

In a previously published paper (Oosterveld, 1970) we described the fact that higher g values, which means an otolithic stimulation, were able to arouse a PAN even if the amount of administered alcohol was very small and even if the moment of the application of alcohol was more than 12 hours prior In weightlessness, a PAN disappears immediately These findings also point in the direction of a specific role of the otoliths in the genesis of alcohol nystagmus. Nevertheless, a nystagmus is not the usual response following otholitic stimulation.

In a previous publication the hypothesis was stated that the otoliths modulate a centrally provoked nystagmus both in amplitude and direction depending on the position in space During intoxication with alcohol a nystagmus tendency is continuously present and it is only released in certain positions. These views agree with those of Aschan et al. (1964 1965) and Grant et al. (1964) that the place of the origin of PAN must be searched more centrally

The otoliths or the utricle seem to play an essential role in the trigger mechanism of the appearance of alcohol nystagmus.

RÉSUMÉ

Le nystagmus vestibulaire joue un rôle très important dans l'origine du nystagmus de position provoqué par intoxication alcoolique (P.A.N.). Une investigation a été faite chez le lapin concernant l'effet des lésions artificielles labyrinthiques sur le P.A.N. Avec seulement les canaux semi-circulaires intacts il n'était pas possible de produire un P.A.N Chez les lapins ayant subi une destruction labyrinthique unilaterale on pouvait encore provoquer le P.A.N Si par contre on sectionnait le nerf utriculaire du côté non opéré il était de nouveau impossible de produire le P.A.N. Le fait que la partie statique du système vestibulaire est responsable pour le P.A.N est confirmé par l expérience que le P.A N est fortement influencé par des accélérations linéaires aussi bien chez le lapin que chez l'homme.

ZUSAMMENFASSUNG

Der Vestibularapparat spielt eine grosse Rolle beim Entstehen eines Alkohol-Lage-Nystagmus (P.A.N.). Eine Untersuchung wurde gemacht zur Beurteilung des Effekts künstlich hergestellter Läsionen des peripheren Vestibular Organs bei Kaninchen. Wenn nur die Bogengänge noch intakt waren, war es nicht mehr moglich ein P.A.N zu erregen. Bei Kaninchen mit einseitiger Labyrinth-Zerstörung war es aber moglich einen P.A.N zu erregen. Wenn aber bei diesen Tieren der Nervus utricularis an der Seite der Labyrinth-Zerstörung durchschnitten worden war war es nicht mehr möglich einen P.A.N zu erregen. Dass der statistische Teil des Gleichgewichtsorgans verantwortlich ist fur den Alkohol-Lage-Nystagmus wird auch bestätigt durch den Befund, dass geradlinige Beschleunigungen in hohem Masse einen P.A.N beeinflussen konnen, bei Kaninchen so wie auch bei Menschen.

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A TORSION SWING TEST

LEFT SIDE POSITION

B PARALLEL SWING TEST

RIGHT SIDE POSITION

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C P.A.N

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Group VI

The rabbits of the last group had one labyrinthectomized ear and one sectioned utricular nerve on the other side. None of these animals showed a PAN nor when the alcohol dosage had been doubled. Here neither vertical nor rotatory eye-movements were noted (Fig. 5). Table I shows the combined results of all the experiments.

Table I

RABBITS	RESPONSES ON VESTIBULAR TESTS									PAN		
	ROTATION TEST			LINEAR ACCELERATION TEST			CALORIC TEST			PRESENT		ABSENT
	RESPONSE			RESPONSE			RESPONSE					
	NO NYSTAGMUS PREPONDERANCE	NYSTAGMUS PREPONDERANCE	NO RESPONSE	NO PREPONDERANCE EFFECT OF SIDE POSITIONS	PREPONDERANCE EFFECT OF SIDE POSITIONS	NO RESPONSE	BOTH SIDES	ONE SIDE	NO RESPONSE	EQUAL EFFECT OF SIDE POSITIONS	NO EQUAL EFFECT OF THE POSITIONS	
NORMAL	•			•			•			•		
LABYRINTHECTOMIZED ON ONE SIDE		•			•			•			•	
LABYRINTHECTOMIZED ON BOTH SIDES			•			•			•			•
UTRICULECTOMIZED ON ONE SIDE	•				•		•				•	
UTRICULECTOMIZED ON BOTH SIDES	•					•	•					•
UTRICULECTOMIZED ON ONE SIDE AND LABYRINTHECTOMIZED ON THE OTHER SIDE		•				•		•				•

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EFFECT OF REPETITIVE OPTOKINETIC STIMULATION UPON OPTOKINETIC AND VESTIBULAR RESPONSES

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Abstract. The question of whether habituation of optokinetic nystagmus occurs with repetitive stimulation was studied in a series of trials in 15 human subjects. The results indicate that there is no response decline characteristic of habituation, but on the contrary a constant and definite increase of optokinetic response, interpreted as the result of a *positive learning* process. The latter does not influence or modify the caloric, rotatory and galvanic vestibular responses.

Repetitive stimulation of a sensory organ may induce *habituation* which, according to the definition of Thorpe (1950) represents a simple process of learning not to respond to stimuli, which tend to be without significance in the life of the organism. The term of habituation, introduced by Abels (1906), is generally used to indicate the phenomenon of a progressive response decline to repeated stimuli, having identical parameters (Monnier et al., 1970). Habituation of the vestibular system by various sorts of stimuli (rotatory caloric) has been reported by many authors (Hood & Pfaltz, 1954 Henriksson et al., 1961 Fluur & Mendel, 1969 Guedry 1964 Forssman, 1964 Forssman et al., 1963 Brown & Crampton, 1965 Collins, 1965 1966 Aschan, 1967 Pfaltz & Pilfko 1970 1970 Monnier et al., 1970 Montandon et al. 1970 Gremer et al., 1970 Pialoux et al., 1970 Kaphan, 1970). However reports on the habituation of optokinetic nystagmus are scarce and contradictory Fernández & McClure (1963) could not confirm the presence of a progressive decline of optokinetic responses in man following repetitive optic stimulation. On the other hand, Oku (1954), Motohasi (1965), Shiraki (1967) and Hinoki et al. (1971), based upon animal experiments, reported a gradual increase of optokinetic responses after repeated optic training.

The question arises, whether any modification of the optokinetic responses induced by repeated optic stimulations of varying intensity and direction, may be observed in normal human individuals. If such a modification of the optokinetic responses could be confirmed, it would involve the question whether this modified response were the result of *habituation* or of some other learning-mechanism. Another question is, whether vestibular responses might be modified by repeated optokinetic stimulation. We have made an attempt to approach this very complex problem by carrying out the following experimental study

Test procedure

The observations were made on 15 healthy well motivated subjects, with an age range from 14 to 45 years. None of the subjects had any gross abnormality of vision or eye motility

The instrumentation used for eliciting optokinetic nystagmus consisted of a Bárány type drum (B.T.D.) on the one side (Fig. 1) and a Jung-type projector-screen (J.T.P.S.) on the other side (Fig. 2). The former was used

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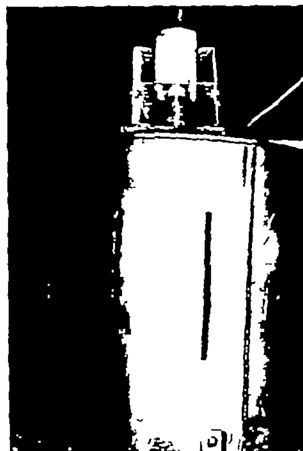


Fig. 1. Bárány Type Drum. This apparatus is a modification of the optokinetic stimulator designed by J. Lang (1962), consisting of a metal box, which contains a metal cylinder driven by an electromotor. On the case of the cylinder 10 circular perforations (2 cm diameter) are set at equal distance, illuminated by an electric lamp from the inside. They produce well-circular light spots on a ground glass screen, on a rectangular window (2.5 10 cm), which on the front side of the metal box. The tance between circular perforations implies that only one light spot will appear on the screen at any time. The test subject, whose head is fixed on a metal support (distance head stimulator 57 cm) is asked to follow the light spots passing in front of him. With this stimulating device only foveolar optokinetic nystagmus is induced because merely one target (light spot) is moving across the test subject's visual field at any time.

for eliciting foveolar nystagmus by narrow angle-target stimulations, the latter for eliciting both foveolar and peripheral (retinal) optokinetic nystagmus (OKN) by wide-angle target stimulation. Foveolar OKN is induced by an angular velocity of the wide-angle tar-

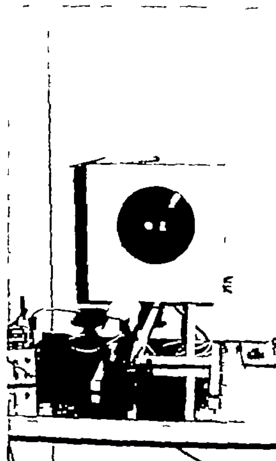


Fig. 2. Jung Type Projector Screen. A metal cylin with 12 slots, set at equal distance (30°) driven an electromotor is projecting dark and light stri on a white half cylindrical screen (diameter 160 c The projector is located and rotated above the he of the test subject, who is in front of the screen a distance of 80 cm. The length of the project stripes is 80 cm and the width 3 cm, correspondi to a visual angle of 57° and 2.1 respectively.

gets <90 /sec, whereas any target spe >90 /sec will initiate only peripheral OK (Miyoshi, 1970).

Recording of eye movements: different photoelectric nystagmography (Pfaltz & Ric ter 1955 1956) and by means of a speci d.c. recording design (Richter et al., 196 which is free of deformities of the tracings.

Habituation test series

One trial, repeated on 10 successive days, co sisting of 10 successive stimulations daily

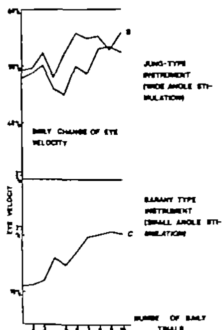


Fig. 3 (*a*) Daily change of eye velocity (velocity of the slow phase of optokinetic nystagmus). Groups A and B (wide angle stimulation) show an irregular but definite daily change of eye velocity resulting in a final increase of optokinetic responses, comparing the results before and after the habituation trials. Group C (small angle habituation) shows a regular definite and constant daily change of eye velocity also resulting in a final increase of optokinetic responses.

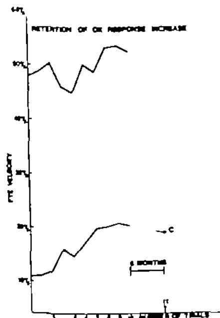


Fig. 3. (*b c*) Retention of OK response increase. In Group B there is no conclusive evidence of retention, whereas in Group C optokinetic responses 6 months

15 sec duration, each followed by a 15 sec recess.

Target movement velocity 30 /sec for B.T D -stimulation corresponding to a small angle stimulation, and 60 /sec for J T.P.S. stimulation, corresponding to a wide angle stimulation.

Before and after each trial the following tests were carried out. caloric test (Hallpike-Fitzgerald method)—stepping test—optokinetic test with target velocities of 15 /sec, 20 / sec, 25 /sec, 30 /sec for B T D and J T P.S. stimulation and 60 /sec, 90 /sec 120 /sec for J T P.S.-stimulation (bidirectional stimulation)

As a parameter for the evaluation of the optokinetic response we have used the velocity of the slow phase.

The 15 test persons were divided into 3 groups (A, B C) of 5 individuals each.

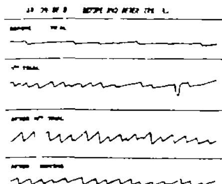
Group A Habituation by J T.P.S.-stimulation *towards the right (direction of target movement).*

Group B Habituation by J T.P.S -stimulation towards the left.

Group C Habituation by B.T.D -stimulation towards the right.

DISCUSSION OF RESULTS

The curves in Fig. 3 *a* and *b* reproduce the average slow phase velocity values of 5 per



after the last trial are still exhibiting a marked increase (3).

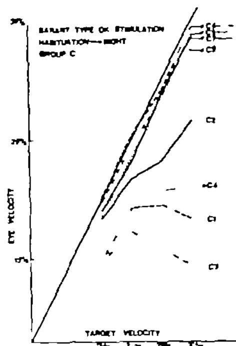


Fig. 4 Habituation to the right by small angle optokinetic stimulation (target velocity 30°/sec.). The target velocity for the control tests is 15 /sec–20°/sec 25 sec–30°/sec.

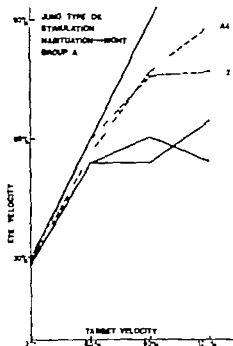


Fig. 5 Repetitive wide angle optokinetic stimulation by a Jung-Type Projector Screen Equipment" (JTPS). For the habituating trials a target velocity of 60° sec is used, for the control tests a target velocity of 30°/sec, 60°/sec, 90°/sec, and 120°/sec.

Figs. 4 and 5.

A/B–1 C–5 control test before trial 1	Optokinetic stimulation
A/B–2/C–6 control test after trial 10	→ R by JTPS
A/B–3/C–7 control test before trial 1	optokinetic stimulation
A/B–4 C–8 control test after trial 10	→ L by JTPS
A/B–5/C–1 control test before trial 1	optokinetic stimulation
A/B–6 C–2 control test after trial 10	→ R by BTD
A/B–7 C–3 control test before trial 1	optokinetic stimulation
/B–8 C–4 control test after trial 10	→ L by BTD

sons belonging to the same group. Optokinetic responses following repeated optic stimulation do not exhibit a response decline but on the contrary a significant response increment. This may be seen from Fig. 3 *a* showing the daily change of the slow phase velocity of optokinetic nystagmus, and also from Fig. 3 *b* demonstrating a *maintenance of this response increment for 6 months* after the last trial.

It is interesting to recognize that the establishment of this response increment is independent of the direction and the varying velocity of the optic training movement. E.g. test subjects habituated to the right were showing an increase of both left and right optokinetic responses, even if different target velocities were used during the trials and for the control tests. Both findings may be interpreted as the result of a *transfer-mechanism.*

Caloric test results did not reveal any conclusive changes after repetitive optic stimulation although the total reaction seems to show some tendency to increase. However further investigations are necessary to come to a final conclusion.

The galvanic test results before and after 10 OKN-trials do not demonstrate any definite response decay or increment, nor the establishment of a directional preponderance,

which might be related to the direction of the optic training movement.

Stepping test

Subjects show an evident tendency to rotate in a direction opposite to the direction of the optic stimulation, applied during the daily trial and corresponding to the quick phase of OKN. In subjects belonging to the groups tested by wide-angle stimulation (Groups A and B) this observation was even more evident and more constant than in Group C, stimulated by small-angle stimulation.

In our experimental study on 15 normal subjects, repeated unidirectional optokinetic stimulations did not result in an *acquisition* of a progressive optokinetic *response decline* a finding which is in agreement with the observations made by Fernández & McClure (1963). On the contrary we observed the opposite phenomenon, i.e. the *acquisition* and *retention* of a very definite *response increment* (Fig. 3 *a*, *b*). Similar observations have already been made by Oku (1954), Hinoki & Terayama (1966) and by Shiraki (1967) in animal experiments. The test procedure of Fernández & McClure (1963), in which they did not observe any response increase, was quite different from ours (constant angular velocity of optokinetic stimulus instead of different stimulation intensities—exposure to only one trial instead of exposure to several trials over a certain period of time). For that reason our results cannot be compared with theirs.

The question arises, whether the increment of the optokinetic response may be interpreted as a true *habituation phenomenon*.

Habituation is a decrement of response with repeated stimulation. It differs from both sensory adaptation and nerve accommodation in its characteristics, and does not depend on the effector fatigue (Sharpless & Jasper 1956, Hernández-Peon & Brust-Carmona, 1961). It is interpreted as the simplest process of *negative learning*.

The occurrence of a *response increase* following repeated optic stimulations of varying intensity cannot be interpreted by habituation. This is in agreement with a statement made by Kornhuber (1966) indicating that habituation of optokinetic nystagmus does not exist.

Optokinetic mechanisms are greatly influenced by alertness. When a small object moves through the visual field of a person, it induces a "grasp reaction" requiring attention (Monnier 1967). The underlying mechanism of this reaction is foveal vision and its resultant foveolar OKN. In our test series, OK response increment and its retention was more marked in subjects exposed to repetitive foveolar optic stimuli (group C, Fig. 4) than in subjects exposed to stimuli involving peripheral vision (groups A and B, Fig. 5). According to Hood (1967) foveal OKN is under the controlling influence of the centre for voluntary gaze in the frontal cortex, while peripheral OKN has a more reflex character and comes under the influence of the occipital visual center. The modification of the OK response, more marked for its foveolar type, may therefore be due to a process of learning, occurring at the level of the cerebral cortex or some other central region of convergence of sensory impulses. If we are accepting Glaser's (1966) definition of learning (acquisition of new responses or a modification of preexistent responses, induced by storage of novel information) we may assume that the increase of optokinetic responses, induced by repetitive optokinetic stimulation or optic training, is the resultant of a positive *learning-process* probably serving the visual system to improve its ability to pick up the periodicity of simple motion patterns, in order to use this sensory information for an improvement of the motor output.

RÉSUMÉ

Le problème de l'habituation du nystagmus optocinétique et son influence sur les réponses vestibulaires a été étudié dans 15 sujets normaux, exposés à des stimulations optiques répétées. Le résultat de cette expérience démontré qu'il n'existe pas d'habituation optocinétique, caracterisée par une diminution des ré-

ponses nystagmiques dans le sens d'un "negative learning process" Par contre, une série de stimulations optiques répétées amène une augmentation nette des réponses optocinétiques, un phénomène qui est interprété comme résultante d'un "positive learning process" Ce dernier n exerce aucune influence sur les réponses vestibulaires thermiques, rotatoires et galvaniques.

ZUSAMMENFASSUNG

Das umstrittene Problem der Habituation oder Gewöhnung des optokinetischen Nystagmus wurde an 15 gesunden Individuen mittels wiederholter optischer Reizungen untersucht. Die Ergebnisse zeigten, dass es keine echte optokinetische Gewöhnung im Sinne der verminderten Reizantwort gibt, sondern dass im Gegenteil am Ende der Versuchsreihe regelmässig eine erhebliche Steigerung der optokinetischen Reizantwort beobachtet werden konnte. Dieses Phänomen wurde als Ausdruck eines *positiven Lernprozesses* gedeutet, im Gegensatz zur Gewöhnung, welche den einfachsten Typ eines *negativen Lernprozesses* darstellt. Letzterer beeinflusst in keiner Weise die vestibulären Reizantworten.

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DISCUSSION

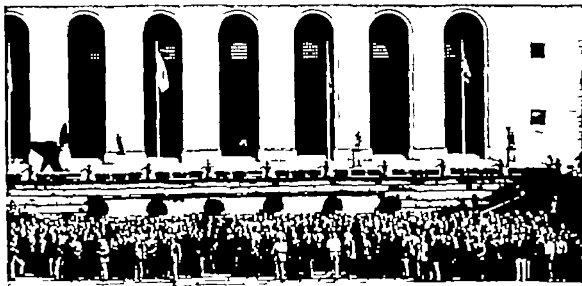
M Hinoki: We too have studied the mechanism of transfer of the effects of repeated optokinetic stimulation to labyrinthine nystagmus. As pointed out by Dr Oka, in Gifu, Japan, when guinea pigs received repeated optokinetic stimulation they showed an increased response in optokinetic eye nystagmus. In parallel with this, they developed a response decline in postrotatory eye nystagmus. We confirmed this type of transfer by using rabbits and fowls. We also found that in rabbits in which the deep nuchal muscles were paralysed with procaine, this type of transfer was not observed appreciably even when adequate optokinetic stimulation was given repeatedly This finding indicates that transfer of the effects of repeated optokinetic stimulation to labyrinthine nystagmus can only develop clearly when the cervical proprioceptors are functioning normally In our experiments using EEG we also found that procainization of the deep nuchal muscles can greatly depress the activity of the activity of the central nervous system and especially the brain stem reticular formation. So, we may conclude from these findings that the brain stem reticular formation can play an important role in the mechanism of transfer of the effects of repeated optokinetic stimulation to nystagmus responses of labyrinthine origin.

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THE XVIII CONGRESS OF THE SCANDINAVIAN OTO-LARYNGOLOGICAL SOCIETY

Göteborg, Sweden, June 28–30, 1972

The Congress was held in Stenhammarsalen, the Concert Hall Göteborg. The program was limited to the following topics.

Pathogenesis and Therapy of Chronic Otitis
Carcinoma of the Oral Cavity
Noise
Traumatology in Otology
Recurrent Nerve Paralyses
Prolonged Endotracheal Intubation.

The President, Professor G. Herberts, addressed the Congress as follows:

On behalf of the Congress Board I have the honour to wish all the members of the Congress from the different Scandinavian countries a hearty welcome to Göteborg.

The programs from earlier meetings during the activity of the Scandinavian Society have reflected the actual research fields of their day and the development of the speciality I wish to remind you that at the first meeting of our Society now sixty years ago the famous Danish otologist Ernst Schmiegelow lectured on the treatment of sequelae of larynx and trachea after tracheostomy while we at this meeting are going to discuss a similar subject, namely lesions after endotracheal intubation instead of tracheostomy We shall also be discussing other oto-laryngological themes, which have been selected after an inquiry among the colleagues. In this way we hope to receive an exposé of the problems of today in our speciality

In the lay-out of the transactions we have tried to pay due attention to expressed wishes and we have also had the ambition to make the various subjects informative and responsive To realize this, it has been necessary to increase the co-ordination of the lectures and arrangements in symposia and panel discussions, modelled by the respective moderator

As in earlier congresses several scientific exhibitions have been arranged to illustrate the various sections.

Collaboration in Scandinavian Otolaryngology is to be discussed at today's business meeting, especially some questions concerning organization and education at different levels. This is of especial interest before the expected reorganisation of the training programs.

It is our hope that the Congress will give a good presentation of the problems and the situation of otology today and make valuable contributions to the development in some important fields. In this way the tradition will be supported that was formed by the great predecessors in Scandinavian otology at the beginning of the century at the time when our Society was founded.

With these words I wish the members welcome to the transactions which will start immediately

Business meeting of the Congress

The President announced the Icelandic invitation for the next Congress to be held in Reykjavík in 1975 The Congress accepted the invitation unanimously and agreed to the proposal that the next Congress Committee should comprise Dr E. Thorsteinsson, President Dr S. Skaftason Vice President and Dr Ole Bentzen General Secretary It was suggested that the Congress should take place on June 29 to July 2, but decisions upon date and program were left to this Congress Committee.

The Icelandic members asked the members of the other Scandinavian countries to support them in the development of oto-rhino-laryngology in Iceland. The Congress recommended the Otolaryngologic Societies and Associations of the different countries to give the Icelandic members all information and support which they might need.

Professor H Engström proposed that educational and examination material at all levels in oto-rhino-laryngology should be exchanged between the different university clinics and other clinics involved in education in the Scandinavian countries. The Congress accepted this proposal and the Department of Otolaryngology in Uppsala was chosen to act as a bank for this material.

Professor H C. Andersen recommended a meeting to discuss education at all levels in oto-rhino-laryngology in the Scandinavian countries. The Congress accepted the idea and Professor Andersen promised to prepare proposals for such a meeting.

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NEW ASPECTS IN THE PATHOGENESIS OF CHRONIC SECRETORY OTITIS MEDIA

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Abstract On the basis of quantitative studies of the mucous elements in the Eustachian tube and middle ear mucosa of normal and abnormal temporal bones as well as of biopsies from secretory and adhesive otitis the secretory pathogenesis is described. Secretory otitis is divided into a stage of development, during which the mucous glands form, a stage of secretion, during which they produce mucus, and a stage of degeneration, during which they degenerate, become inactive, and mucus production decreases The relationship between the ability of the mucosa to produce mucus and the ability of the Eustachian tube to transport the mucus to the rhinopharynx is the essential factor in the secretory pathogenesis.

The transudation" theory or the exudation theory" on the pathogenesis of chronic secretory otitis cannot explain why secretion in the middle ear of children is tenacious mucus which, despite a well-functioning drain, may form again, and why secretory otitis may be present even though there is perforation of the drum and a patent Eustachian tube. We have previously on the basis of quantitative studies of mucous glands in an autopsy specimen, advanced a new secretory" theory on the pathogenesis of the disease (Tos & Bak Pedersen 1972) Continued quantitative studies of the mucous elements in normal and abnormal autopsy specimens and in biopsies from secretory and adhesive otitis have disclosed new findings which confirm and supplement this theory on the pathogenesis. Foetuses have no mucous glands in the osseous tube or in the middle ear Children and adults whose tubal or middle-ear mucosa has never been exposed to abnormal action show only a few glands or none, but a larger number if the mucosa has been exposed to an abnormal action. Since most of the glands become inactive, such ears may be clinically quite normal.

In an autopsy specimen with mild chronic secretory otitis we found 488 mucous glands in different secretory stages (Bak Pedersen & Tos, 1971) and a marked increase of goblet cell density In biopsies from 85 ears with typical secretory otitis and mucus in the middle ear we found mucous glands in all but two (Tos & Bak Pedersen, 1972) The mean density was 7 1 glands/mm² corresponding to about 2 000 glands in the entire middle ear 93% of which were active. The goblet-cell density was greatly increased. In biopsies from 48 ears with chronic adhesive otitis we found a density of 4.3 glands/mm² only 11% of which were active.

The types of glands show given characteristics. A distinct transition from active to degenerated glands was demonstrated. Active glands have well-preserved secretory epithelium, narrow ducts, and no stagnation of mucus in the tubules. Transitional varieties have a somewhat dilated duct system filled with mucus, but the secretory epithelium is still fairly well-preserved in places. Degenerated glands show maximum dilatation, a mucus-filled duct system where the secretory

epithelium has entirely disappeared. The primary factor in degeneration of glands seems to be stasis of mucus flow causing dilatation of the duct system, stretching of and pressure upon the secretory epithelium with degeneration and total disappearance of the mucous cells.

Abnormal glands must form at some stage of secretory otitis, which we call the *stage of development* The histology of this stage has not yet been described, but in biopsies we found some developing young glands. The glands form a link in epithelial metaplasia due to low virulent infection chronic catarrhal state of the tube long-lasting tubal occlusion or recurrent otitis The irritant is presumably chronic or recurrent. At least 1–2 months have to pass before the glands have completed their development When they form mucus, the *stage of secretion* starts, mucus accumulates in the middle ear and causes the well known clinical symptoms. Histology is predominated by active mucous glands and highly increased goblet-cell density The period elapsing until the middle ear has filled with mucus depends upon the secretory capacity (number and size) as well as secretory activity of the glands and not least upon tubal and ciliary function which transports the produced mucus to the rhinopharynx At a slight secretory capacity and good tubal function the produced mucus can be transported to the rhinopharynx, and major accumulations will never occur in the middle ear Conversely with a large number of active glands and poor tubal function the middle ear soon fills, and despite a well functioning drain mucus will regenerate in the course of a month or two The relationship between the ability of the mucosa to produce mucus and the ability of the tube to transport it away from the middle ear is the essential factor in the secretory pathogenesis and explains the varying degrees of severity and duration of the disease However the aetiological factors may cause renewed formation of glands and increased secretory capacity If untreated, the disease enters a vicious circle Accumulation of mucus, exacerbation of tubal occlusion, formation of new glands, and increased mucus production. When the glands start degenerating the disease enters the *stage of degeneration* in which the histology is predominated by the transitional varieties and degenerated glands and during which mucus production decreases. If tubal function returns to normal, the ear recovers, if adhesive otitis has not arisen already The small amounts of mucus produced during this stage may be transported to the rhinopharynx through a well-functioning tube. However in this stage too new glands may form and the mucus production may increase. This explains why the disease may last for a very long time and flare up anew

Quantitative studies of the mucous elements performed so far have shown that the secretory capacity of each gland is so slight that a few active and many degenerate glands in the middle ear are of no clinical importance. At least 200 active glands are required to cause accumulation of mucus. Goblet-cell density also increases during the course of the disease and decreases during the stage of degeneration.

The secretory pathogenesis fully explains the clinical course but not the presence of straw coloured fluid occasionally found in adults. Perhaps there is—unlike the condition in children—a special, more exudative form of the disease

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MIDDLE EAR EPITHELIUM IN CHRONIC EAR DISEASE

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Abstract. Thirteen chronically infected temporal bones were serially sectioned and stained to study the characteristics of any possible squamous epithelium. Non-cholesteatomatous epithelium is either immigrative or metaplastic in origin and the cholesteatomatous always immigrative. The metaplastic epithelium does not keratinize and the non-cholesteatomatous immigrative slightly keratinizing type may change into cholesteatomatous aggressive type only in the presence of at present unknown inductors.

The purpose of this paper was to examine systematically in serial sections the middle ear epithelium in chronically infected temporal bones, to study the characteristics and origin of the squamous epithelium, and to relate the epithelial changes to tympanal pathology in general. The material consists of 13 temporal bones, fixed in 10% formalin and decalcified with 22.5% formic acid-sodium citrate solution. After celloidin-paraffin embedding, the blocks were sectioned and stained by various methods for general characteristics, for mucosal secretory components and for epithelial phospholipids (Karma, 1972).

The middle ear epithelium in cases of chronic infection showed hypertrophy hyperplasia, secretory proliferation and squamous metaplasia. Immigrating squamous epithelium, epidermization and even epidermosis were also encountered in this material. Sometimes the opposite was the case: the tympanal epithelium emigrated to the outer surface of the drum membrane.

As a rule respiratory often secreting epithelium lined the middle ear cavity widely in its anterior and inferior parts, extending in many ears to the inner surface of the tympanic membrane, to the epitympanum, posterior tympanum, and even to the area of the mastoid air cell system. The tubotympanic ciliated epithelium continued posteriorly in the form of one to four narrowing strips which were located mainly inferiorly and extended in some ears up to the posterior limits of the middle ear cleft.

Metaplastic columnar and squamous epithelium in various stages occurred in all ears; however the metaplastic stratified squamous epithelium never showed any signs of keratinization.

All epidermal layers of the immigrating stratified squamous epithelium, except rete pegs, were seen at least in the area of the perforation edge. The junction between the epidermis covering the tympanic membrane remnants and the tympanal epithelium varied from very abrupt change to a gradual change with a transitional area of varying length. In some ears the junction showed keratinizing squamous epithelium and columnar ciliated epithelium side by side and sometimes the squamous epithelium lost its keratinizing properties before it joined the tympanic columnar epithelium. In other ears the squamous epithelium grew for a short distance under the columnar epithelium and pushed it aside. In some cases it also grew for some tenths of a millimetre over the columnar epithelium. In 6 temporal bones the epidermis sent extensions deeper into the subepithelial area near the junction.

In cases with gradual changes the transitional epithelium had a length of 0.1 to 2 mm in the junctional area. The transition often occurred gradually through various parakeratotic and pseudoparakeratotic stages, first into metaplastic and later into columnar and cuboidal epithelium The epidermal immigration was of the least extent in central perforations whereas total pars tensa defects showed wide immigration into the tympanum and to the promontory The epithelium covering the promontory was squamous in 6 cases in 3 it was clearly immigrative and in 3 metaplastic.

The immigrating squamous epithelium retained its slight keratinizing properties in the tympanum and changed, in only one case into aggressive-looking hyperkeratotic and acanthotic epidermoid epithelium showing subepithelial extensions. Except hyperkeratosis there were no other definite histological differences between these two types of squamous epithelium.

It is obvious from these studies of serially sectioned temporal bones that in chronically infected middle ears the mucosa almost always shows areas of squamous epithelium of varying extent It may be immigrating, less often metaplastic and it can retain its non-cholesteatomous character throughout the duration of life

Transition from ciliated into squamous epithelium and vice versa, and large differences in keratinization have been described in experimental studies (McLoughlin, 1961). It is possible that mesenchymal factors play an important part in epidermal differentiation and keratinization

These data confirm the findings of Palva et al. (1968) that there exist various types of squamous epithelium in chronically infected middle ears. Serial sections suggest that the non-cholesteatomatous type of squamous epithelium is either immigrating or metaplastic in origin and that the cholesteatomatous type is always immigrative The metaplastic type does not undergo keratinization the non-cholesteatomatous immigrative type may retain its properties of slight keratinization permanently and does not change into cholesteatomatous aggressive, expansive epithelium, a process which is still poorly understood at present.

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DENSITY OF MUCOUS GLANDS IN VARIOUS CHRONIC MIDDLE EAR DISEASES

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Abstract From 491 operated ears 5 180 pieces of mucosa from 16 different middle-ear sites were stained by the PAS-alcian blue whole-mount method and the density of glands in each piece determined. The mean density of glands was greatest in secretory otitis, 7 1 glands/mm² in dry adhesive otitis, 4.3 in chronic, infected, adhesive otitis, 3 4 in chronic granulating otitis, 2.0 in cholesteatoma and sequelae to otitis, 1.3 in tympanosclerosis, 0 6, and in otosclerosis, 1 7 The differences in glandular density and the predominance of the various secretory types were found to be characteristic of the various middle-ear diseases.

Research into the histopathology of the human middle-ear mucosa in various chronic middle-ear diseases has increased during recent years. This research has been based partly on biopsies (Bendek, 1963 Sadé & Weinberg, 1969) and partly upon post-mortem studies of temporal bones (Sadé, 1966 Bak Pedersen & Tos, 1971) and has been concerned *int al.* with the mucous elements of the middle-ear mucosa —glands and goblet cells—which have been demonstrated by most authors. However apart from Bak Pedersen & Tos study from 1971 the investigations conducted so far have been on sections which do not permit an exact quantitative determination of the mucous elements. The present study was carried out by a special whole-mount technique which makes it possible to determine the density of the mucous glands, expressed as glands/mm² in the various middle-ear diseases as well as a more accurate morphological assessment of the individual glands. Such quantitative studies have not been published previously

MATERIAL AND METHOD

The material comprises 491 ears (Table I). The investigated pieces of mucosa were removed in various otosurgical procedures from 16 different sites in the middle ear and from 1–10 localities per patient. The number of biopsies depended upon the extent of the operation, the study being restricted to mucosa which was to be removed anyway A total of 5 180 mucosal pieces were studied. The tissue pieces were stained by the PAS-alcian blue whole-mount method (Tos, 1970) Under the stereomicroscope the mucous glands were counted, the area of the tissue pieces measured, and the density (glands/mm²) calculated, for each locality as well as for each ear

RESULT

For all ears 6 331 mm² mucosa was counted and showed 13 325 glands. Of this number 20% were active glands with PAS-alcian blue positive secretory epithelium and narrow tubular lumina without stagnant mucus. 31% were large glands showing cystic degeneration with flat epithelium devoid of secretory activity marked dilatation of the tubules and excretory duct, as well as stagnation of mucus.

Table I *The material studied*

	No. of ears	No of studied sites	Total no. of glands	Total area (mm^2)	Mean density (glands/mm^2)
Secretory otitis	85	85	743	105	7 1
Dry adhesive otitis	48	151	1 855	424	4.3
Chronically infected adhesive otitis	30	105	2 539	752	3 4
Chronically granulating otitis	93	316	5 166	2 612	2 0
Cholesteatoma	70	241	1 982	1 510	1.3
Sequelae to otitis media (dry)	95	189	873	682	1.3
Tympanosclerosis of tymp. cav	26	47	60	184	0.6
Otosclerosis	44	56	107	62	1 7
Total	491	1 190	13 325	6 331	

49 6% were transitional varieties between the active and the degenerated glands, but showing degeneration of the greater part of the secre tory epithelium The ratio between active and degenerated glands in secretory otitis showed a great predominance of active glands (93%). In adhesive otitis, chronic granulating otitis, cholesteatoma, and sequelae to otitis the active glands made up only 8–20% in tympanosclerosis there were but few and in otosclerosis no active glands. The remainder were transitional varieties and degenerated glands.

The mean density of glands was greatest in chronic secretory otitis and least in tympanosclerosis (Table I) Within the individual disease groups there was quite considerable dispersion of the density partly in the different middle-ear sites, and partly between the different ears. The widest range was observed in adhesive otitis which showed in one site (annulus posteriorly) a range of from 0–68 glands/mm^2

The density of glands, and especially the ratio between active and inactive glands, form part of a given pattern of the histopathology of the middle-ear mucosa in the various middle-ear diseases. The secretory activity and the secretory capacity of the glands are of significance in the treatment and prognosis of the various middle-ear diseases.

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CICATRICIAL CHANGES OF THE EARDRUM AFTER TREATMENT WITH GROMMETS

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Abstract. 79 of 117 patients, treated with grommets for chronic secretory otitis media, developed cicatricial changes (atrophy or/and fibrosis) of the ear drums. 38 of these patients had only minor changes at the former grommet site. Atrophic drum was related to a "negative" middle ear pressure (i.e. dysfunction of the Eustachian tube). Fibrosis of the drum, in some cases in combination with atrophy, was found more frequently among patients with long drainage time. Hearing was not affected in any of the groups.

One of the problems in the treatment of chronic secretory otitis media by transmyringeal drainage with plastic tube (grommet) is: does the treatment produce cicatricial changes of the eardrum and if so, do these affect hearing? In a retrospective investigation with follow-up examination of patients treated with grommets, we have tried to explore this problem.

MATERIAL AND METHOD

The material includes 117 patients (188 ears) treated with grommets (i.e. tubulation) for chronic secretory otitis media. (In total 146 patients were treated, 29 absented themselves from follow-up and are not included in the material.)

Of the patients 108 were children and young teenagers (< 15 years). The age distribution had concentration around 3–4 years (at the moment of tubulation). Two-thirds of the patients were males. Average observation time (i.e. time from extrusion of the grommet to follow-up) was 22 months.

The follow-up examination included otoscopy with classification of present cicatricial changes of the eardrums as listed in Table I (using the common name cicatricial for both atrophic and fibrotic changes). Furthermore, audiometry, tympanometry by impedance bridge, examination of stapedius reflex and (usually) inspection and photography of the ear-drums by the operation microscope.

The data of right and left ear in the binaurally treated patients (71 persons) showed significant concordance. In order to avoid falsely significant results only one set of data were used from each patient (one of the ears selected at random).

RESULT

Seventy-nine of 117 patients developed cicatricial changes of the eardrums between the first examination at the clinic and follow-up (Table I).

By examining the dependence between the groups listed in Table I, and parameters considered by us to play a possible role in the development of the cicatricial changes, the following results were obtained.

The more severe cicatricial changes (groups 2–8) were found in all age groups with a frequency of 30–50%. Fibrosis dominated in patients treated at an age under 3 years, while atrophy was more frequent in the higher age groups.

Table I *Classification and distribution of the cicatricial changes developed during or after tubulation*

	No. of pats.
1 Minor changes at the former grommet site	38
2. Isolated small atrophic scar	3
3. Large atrophic scar	1
4 Atrophic drum	10
5 Slightly fibrotic drum	14
6. Severely fibrotic drum	1
7 Mixed fibrosis and atrophy slight degree	11
8 Mixed fibrosis and atrophy severe degree	1

Atrophy of the eardrum (group 4) In this group 80% of the patients had a "negative" middle ear pressure (less than −200 mm water) against average for all patients, 29% Average drainage time was 5 8 months in the atrophy group against average for all patients: 6.3 months.

Fibrosis of the eardrum (groups 5–6) Middle ear pressure was "negative" in only 20% of the patients while average drainage time in this group was 7.3 months.

Mixed fibrosis and atrophy (groups 7–8) In this group middle ear pressure was found to be "negative" in 33% of the patients. Average drainage time was 9 0 months.

Anamnestic duration of symptoms, repeated tubulation suppuration during drainage and sex showed no relation to type or degree of the cicatricial changes of the eardrum.

Hearing at follow-up was not affected in any of the larger groups (4 5+6 and 7+8) An average hearing loss of 10 dB was found in each of the groups as well as in the whole material. The stapedius reflex could not be released in 80% of the patients in the atrophy group in 30% of the patients in the fibrosis group and in 55% of the patients in the group with mixed fibrosis and atrophy

DISCUSSION

Atrophy of the eardrum seems to be connected with a "negative" middle ear pressure, probably as a result of impaired function of the Eustachian tube. Average drainage time and number of tubulations in the group with atrophic drum did not exceed the average for the whole material, indicating that the grommet plays hardly any part in producing this type of change.

Our results suggest that development of fibrosis of the eardrum may be a side effect of treatment with grommets. This conclusion is drawn from the fact that average drainage time was longer in the group with fibrosis and the group with mixed fibrosis and atrophy than in the whole material. In the mixed group horseshoe hyalinosis" was a characteristic finding: a thickened (hyalin fibrotic) part of the eardrum around an atrophic area, the former grommet site (MacKinnon, 1971).

In conclusion, treatment with grommets eliminates the "negative" middle ear pressure, but a risk of development of fibrosis of the eardrum may exist.

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TYMPANOMAXILLARY SHUNT

Experiences and Development

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Abstract Various late complications have occurred in 6 patients following insertion of a tympanomaxillary shunt. The most common of these, slipping and displacement of the shunt, can probably be prevented by using a prefabricated curved tube, by fixating the sutures with silastic adhesive and by putting the tube outside the bony canal wall. This appears to be the only reported method of tubal by-pass which restores middle ear ventilation leaving the canal skin and ear drum intact and which allows the patient to autoinflate by performing Valsalva's manoeuvre.

Tympanomaxillary shunt (TMS) was introduced in 1967 (Drettner & Ekvall, 1967 1969 1970) as a method of reestablishing the aeration of the middle ear in cases with chronic obstruction of the Eustachian tube A silicone rubber tube is placed from the anterior part of the middle ear to the maxillary sinus, running above the temporomandibular joint and medial to the zygoma. The ear drum and the canal skin remain intact after the operation.

After insertion of the shunt the patient can maintain middle ear ventilation by performing Valsalva's manoeuvre which is not possible in patients treated by insertion of an indwelling tube through the drum.

Indication for TMS

Chronic obstruction of the Eustachian tube which has failed to respond to conventional methods of treatment.

Contraindications

Age (not before puberty).

Recurrent infections of the nose and/or paranasal sinuses (patients with a cleft lip and palate are thus usually not suitable for TMS).

Hypoplasia of the maxillary sinus.

Radiotherapy tumour doses to the operative area (e.g for nasopharyngeal malignancies).

Active middle ear infection (e.g. discharging chronic otitis).

This work was supported by the Swedish Medical Research Council (Proj No 17X 749).

Material

To date the operation has been performed on 6 Swedish patients. Furthermore, a few similar operations have been performed in the United States (Glasscock, 1971 Joseph, 1971). The Swedish patients were aged 15 to 47 years at operation and the length of follow-up varied between 5 $^1/_2$ years and 1 year

Results and complications

Restoration of middle ear ventilation together with hearing improvement was achieved in the early postoperative period in all patients. However 1 patient developed autophonia. This disappeared when the shunt, which was wider than in the other cases, was replaced by a narrower one.

Several complications have occurred in the late postoperative period. Slipping of the shunt in the ear canal has occurred in 3 patients. All these patients had a straight tube placed in a groove in the ear canal and bent at the zygomatic root at operation After 1–5 years the tube became displaced and lost contact with the bony canal wall, perforating the canal skin In 2 of these 3 patients the shunt was extruded through the tympanic membrane These

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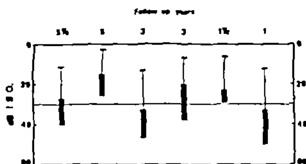


Fig 1 Hearing results in 6 patients with tympano-maxillary shunts. Pre and postoperative hearing are given as means of the frequencies 500 1 000 and 2 000 Hz. Filled bars indicate the hearing gain. Horizontal line indicates bone conduction threshold.

2 cases were revised, one with implantation of a new shunt and the other with removal of the shunt 3 years after the first operation In the latter patient the middle ear was found to be aerated after removal of the shunt showing that while the TMS was in place the function of the Eustachian tube had recovered. The third patient with a displacement of the shunt has at present only a small area of the shunt which is uncovered by the canal skin, and as it is still in a satisfactory position in the middle ear no revision is indicated.

One patient developed recurrence of his adhesive otitis 6 months after insertion of the TMS. At revision the shunt was found to be patent but the silicone rubber sheet was displaced posteriorly

A more serious complication was a long-lasting middle ear infection following acute sinusitis that occurred in one patient 6 months after insertion of the TMS. This patient was a case of ectodermal dysplasia with generalized dermatological manifestations and low resistance to infections. The TMS was removed.

At present the hearing level in all patients shows improvement (Fig. 1)

Technical improvements of the method

Early on in the development of the TMS technique it was realized that there was a risk of late displacement of a straight tube placed in a groove of the ear canal and bent at the zygomatic root even if it was fixed by sutures Before this risk became a reality a special curved tube was designed and is now manufactured (Extracorporeal Medical Specialities, King of Prussia, Pennsylvania USA). This tube has an outer diameter of 2.5 mm and an inner of 1.2 mm. Silastic Medical Adhesive (Dow Corning Corporation, Midland, Michigan, USA) can also be used in conjunction with the sutures around the tube to prevent slipping of the sutures. Furthermore the surgical procedure has been modified in the more recent operations. The tube is now positioned to run from the anterior part of the middle ear into the pretympanic recess, through the anterior part of epitympanum up to the zygomatic root and it therefore mainly lies external to the preserved bony canal wall. These 3 steps (curved tube silastic adhesive and surgical position of the TMS) will probably reduce the risk of displacement of the shunt

The risk of middle ear infection cannot be reduced by these precautions. This stresses the contraindication of using a TMS in patients with a history of recurrent infections of the nose and/or paranasal sinuses.

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TOTAL MIDDLE EAR RECONSTRUCTION

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Abstract Surgical technique and postoperative results are reported in 56 cases of total middle ear reconstruction in classical radical cavities. In 93% of the cases a normal or nearly normal anatomy of the drum and the ear canal was achieved, permitting the patient to swim. 83% reached the 30 dB level post operatively or closed the air-bone gap to within 10 dB. The results were better in cases with remanent mobile stapes than in cases without stapes super structure.

Tympanoplasty in radical cavities involves 4 main problems:

1 *A definitive cleaning* of the cavity and of the middle ear is a prerequisite of "closing" a previously "open" cavity

2. *Reconstruction of a normal external auditory canal* gives the patient a self-cleaning ear that will tolerate swimming, etc.

3. *Restoration of ventilated spaces* in the middle ear and in the mastoidectomy cavity is essential for the functional as well as for the anatomical result.

4 *The sound transmission mechanism* has to be restored.

METHOD

Through a retroauricular incision the cortical opening of the cavity is exposed, care being taken not to injure any uncovered dura or sigmoid sinus. If possible the squamous epithelium of the cavity and of the middle ear should be dissected in continuity to avoid residual disease Preoperative staining of the cavity with 2% gentian violet will facilitate this step The part of the meatal skin that turns posteriorly and superiorly inside the meatal orifice is resected to prevent postopera tive skin pockets. Any remaining infected mastoid cells are exenterated. Care is taken to save as much as possible of the mucous membrane of the middle ear especially in the oval window niche and in the Eustachian tube orifice. Following cleaning, the cavity and the middle ear are lined with Silastic sheeting, which should reach down into the Eustachian tube orifice and posteriorly and superiorly cover the sinal and the dural plates. This will secure a large ventilated cleft from the tubal orifice to the periphery of the cavity and counteract postoperative retraction pockets. Through an aperture in the Silastic a 6–8 mm high "boomerang"-shaped columella, prepared from cortical bone or ossicular homograft, is placed on the centrally denuded stapes foot plate. In cases with a fixed footplate and in most draining ears columellization is left for a second-stage operation. If the walls of the oval window niche are denuded of mucoperiosteum the long leg of the columella is partly covered with a 1.2 mm slitted Silastic tube to prevent bony fixation. In the case of

Table I

Healed drum and ear canal	51 (93)	
Postoperative perforation	0	
Postoperative cavity (intentional)	2	(7%)
Postoperative retraction	3	

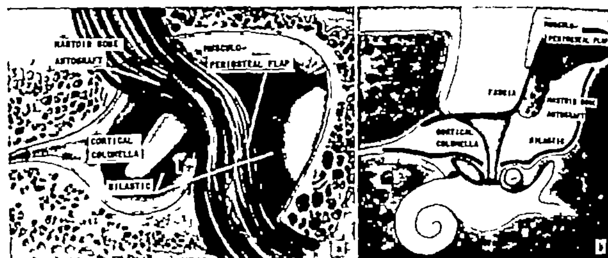


Fig 1 (a b) Schematic drawings to illustrate the surgical technique of total middle ear reconstruction in a classical radical cavity

a remaining mobile stapes a "boot"-shaped columella is used. The middle ear is filled with Gelfoam and dry temporalis fascia is used as tympanic membrane graft. The graft is placed medial to the annulus anteriorly and inferiorly Posteriorly and superiorly the fascia reaches the remaining part of the external canal. The bony canal is completed with an autograft usually taken from the apex of the mastoid process. The graft is placed in grooves the remaining parts of the bony canal and is supported by a double-pedicled musculo-periosteal flap which also bridges the gap be tween the bone graft and the meatal orifice. The canal is packed in two layers with strips of surgical rayon and synthetic fibre wad The pack is left in place for 7 days and then cortisone-antibiotic ear drops are applied locally until epithelialization is completed. Postoperative Eustachian tube function is followed and is supported if necessary

Table II

Serviceable hearing or air-bone gap	> 30 dB I S O < 10 dB	
Total (*n* = 53)		44 (83)
Stapes (*n* = 17)		16 (94)
Footplate (*n* = 36)		28 (78)

RESULT

Anatomical and functional results in 56 consecutive cases with an observation period of between 3 years and $^1/_2$ year are shown in Table I and II. In two of the cases the mastoidectomy cavity was intentionally left open owing to very large and adhesive dehiscences

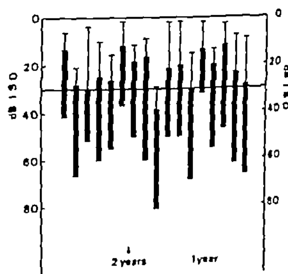


Fig 2 ( ) Individual hearing results in 17 cases with a remanent mobile stapes. ■ hearing improvement □ hearing impairment. Postoperative bone conduction level is indicated by a horizontal line. The values are given as means of the speech frequencies.

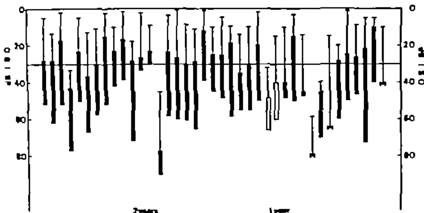


Fig 2 (*b*) Individual hearing results in 36 cases with the stapes footplate as the only remaining ossicle. Caption as in Fig. 2 a.
▲ ossiculoplasty revision;
■ intentional second stage;
● only first stage performed.

of the facial nerve canal. Two cases have postoperative retraction pockets with accumulation of squamous epithelium debris. Fifty-one ears have normal or nearly normal ear canal, permitting the patients to swim, etc. (Table I) In 53 cases an attempt to reconstruct the sound transmission mechanism has been made (Table II). In 3 cases this is planned at a second-stage operation. Six cases, all without stapes superstructure, have undergone an ossiculoplasty revision via a tympanomeatal flap Dislocation of the columella was found in 3 cases, secondary bony fixation of the footplate in 1 case, resorption of the long leg of the columella in 1 case, and severe fibrous adhesions in 1 case. Table II shows the final hearing results so far The less favourable results in the group with the stapes footplate as the only remaining ossicle, when compared with those in the other group, suggest that a mobile stapes from a functional point of view is the most valuable ossicle in tympanoplasty

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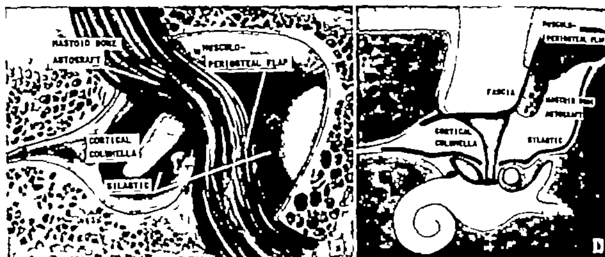


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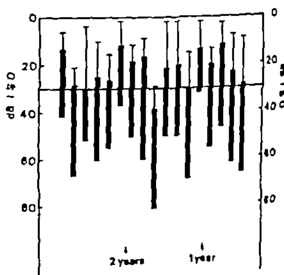


Fig 2 (*a*) Individual hearing results in 17 cases with a remanent mobile stapes. ■ hearing improvement; □, hearing impairment. Postoperative bone conduction level is indicated by a horizontal line. The values are given as means of the speech frequencies.

tween the drum and the stapedial plate the foot of the prosthesis was strengthened by means of a steel wire.

In control examinations it could be ascertained that the cartilage homograft heals in excellently In 6 cases the healing was disturbed by postoperative infection but this seldom occurred because of the reconstruction materials used. A large perforation was found in these cases shortly after the operation. Two ears were checked 16 and 20 months respectively after the primary surgery (myringoplasty) because of an unsuccessful hearing result, and in 15 ears out of 103 (14 6 %) 3 perforations have subsequently healed spontaneously The percentage is high but it should be kept in mind that ears with the largest perforations were chosen for cartilage myringoplasty As parts of the sound conducting system the 8 grafts used have proved agreeable.

According to our experience the homoplastic septal cartilage is a serviceable alternative for use as reconstruction material of the eardrum, especially in cases of large or total perforation. The healing of the graft is good, and quite obviously the method really helps to retain the tympanic cavity in correct shape. It can be considered as an additional advantage that no extra operation is necessary in order to obtain the reconstruction material. The cartilage was also found to be serviceable for the reconstruction of the ossicular chain, but there was no evidence of any superiority compared with, for instance incus autografts or homografts.

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SECONDARY OPERATIONS FOR MIDDLE EAR INFLAMMATION

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Abstract Twelve per cent of operations for chronic middle ear inflammation during the period from May 1969 to Dec. 1971 were secondary operations. Among these 98 ears 33 recidivant of secondary acquired cholesteatomata were found. Several factors were considered to contribute to the need of secondary operations. Relevant preoperative treatment, meticulous operative technique and permanent follow-up are recommended as prerequisites of surgery for chronic middle ear cleft inflammation.

Of 1 206 middle ear operations performed during the period May 1969 to Dec. 1971 at the University Hospital of Turku 98 were secondary operations with an inflammatory middle ear disease as indication The frequency of secondary operations was 12.1% taking into account only operations for chronic inflammation. Table I describes the patient series. In Table II the preoperative indication for the secondary operation is reported in relation to the findings at this secondary operation Findings at the secondary operation confirmed by histopathological specimens are classified in five different types.

(1) Recidivant or secondary acquired cholesteatoma of the middle ear cleft.

(2) Chronic disturbing inflammatory reaction in the operatively created cavity of the middle ear

(3) Recidivant inflammatory process in tympanal or and mastoid region of the middle ear cleft.

(4) Scarring causing disturbances to the normal self-cleaning mechanism or significantly impaired hearing

(5) Recidivant perforation of the drum.

Of the 98 secondary operations, 72 were second, 23 third, 2 fourth and one a fifth operation for inflammation on the same ear In all cases, a detailed analysis was made of circumstances and findings before the primary operation, at the primary operation and during the interval between the primary and the secondary operations. All this information was compared with findings at the secondary operation and the cases were fitted in one of the five types according to the above scheme.

As can be seen from Table II, in 16 cases the diagnosis of recidivant cholesteatoma was the main indication for the secondary operation In 17 cases only continuing inflammation or disturbing scar formation requiring a reconstruction were the indication for the secondary operation which revealed a secondary cholesteatoma.

Main emphasis is paid to recidivant cholesteatoma as it represents a process that will always grow further and as such is often an absolute indication for operative treatment. Thirty three recidivant cholesteatomata were found among these secondary operations. Fourteen of these were considered to belong to the residual type, 12 to the recurrent or migration type and 7 to the iatrogenous type of cholesteatoma (Turner 1970) At the primary operation cholesteatoma was found in only 15 of 33 cases In 5 exact information is not available and in 13 only chronic inflammation without cholesteatoma was revealed by the primary operation When the type of primary operation was analysed in this group of secondary cholesteatomata, it was shown that any type of middle ear operation may be followed by secondary cholesteatoma. The recurrent or migration type of cholesteatoma is most often

Table I. *Age distribution of patients at secondary operation*

	Number of ears						
	<6	7–10	11–15	16–25	26–40	41–60	Totals
Female	2	6	11	10	13	9	51
Male	2	6	7	11	15	6	47
Totals	4	12	18	21	28	15	98
					$\chi^2 = 1.52$	D.F = 5	

found after simple mastoidectomy showing that the primary operation was not extensive enough in its type. The frequency of residual cholesteatoma was highest among modified radical operations with cavity obliteration technique. The incidence of iatrogenous cholesteatoma, which means an epithelial implant as a consequence of the operation, was almost equal among all the types of primary operation.

Comparison between recovery after the primary operation and findings at the secondary operation revealed that difficulties with inflammation are very common among patients of this series. Nevertheless there are 17 cases altogether in which no disturbance of healing could be seen after the primary operation 3 of these cases belonged to the recidivant cholesteatoma group. An apparent technical failure in the exact fixing of the fascial transplant in relation to drum remnants was apparent in 13 cases, in 5 of which a cholesteatoma developed.

This type of examination cannot give a numerical estimate of the risk of secondary cholesteatoma or other secondary disturbance in connection with middle ear operations, as the primary operations of our series date from a period of more than 15 years. Our study revealed many factors that influence the appearance of secondary disturbance Surprisingly little accumulation was seen for example in relation to primary operation for a dry ear or for an actively infected ear but again the manner of collection of this material prevents estimating any relative risk in this respect. In the light of this study we consider it always possible that secondary changes, either scar formation or cholesteatomatous degeneration, may occur even after a smooth healing process. The importance of a meticulous technique and careful preoperative treatment is stressed. A patient with chronic middle ear inflammation requires chronic follow-up even after apparently successful surgery A careful follow-up is a prerequisite for surgery of inflammation in the middle ear

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Table II *Preoperative indications of secondary operation in relation to findings at this operation*

Indications of secondary operation	Findings at secondary operation					
	Cholesteatoma	Cavity inflammation	Mastoid-tympanal inflammation	Scar disturbance	Drum perforation	Totals
Continuing inflammation	13	11	21	1	2	48
Secondary myringo-tympanal reconstruction	—	—	1	3	11	15
Ear canal or drum reconstruction	4	1	—	10	—	15
Recidivant or acquired cholesteatoma	16	—	—	—	—	16
Second stage of operation	—	—	—	4	—	4
Totals	33	12	22	18	13	98

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SECONDARY OPERATIONS FOR MIDDLE EAR INFLAMMATION

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Abstract Twelve per cent of operations for chronic middle ear inflammation during the period from May 1969 to Dec. 1971 were secondary operations. Among these 98 ears 33 recidivant of secondary acquired cholesteatomata were found. Several factors were considered to contribute to the need of secondary operations. Relevant preoperative treatment, meticulous operative technique and permanent follow-up are recommended as prerequisites of surgery for chronic middle ear cleft inflammation.

Of 1 206 middle ear operations performed during the period May 1969 to Dec. 1971 at the University Hospital of Turku, 98 were secondary operations with an inflammatory middle ear disease as indication. The frequency of secondary operations was 12.1% taking into account only operations for chronic inflammation. Table I describes the patient series. In Table II the preoperative indication for the secondary operation is reported in relation to the findings at this secondary operation. Findings at the secondary operation confirmed by histopathological specimens are classified in five different types:

(1) Recidivant or secondary acquired cholesteatoma of the middle ear cleft.

(2) Chronic disturbing inflammatory reaction in the operatively created cavity of the middle ear

(3) Recidivant inflammatory process in tympanal or/and mastoid region of the middle ear cleft.

(4) Scarring causing disturbances to the normal self-cleaning mechanism or significantly impaired hearing

(5) Recidivant perforation of the drum

Of the 98 secondary operations, 72 were second, 23 third, 2 fourth and one a fifth operation for inflammation on the same ear In all cases, a detailed analysis was made of circumstances and findings before the primary operation, at the primary operation and during the interval between the primary and the secondary operations. All this information was compared with findings at the secondary operation and the cases were fitted in one of the five types according to the above scheme

As can be seen from Table II, in 16 cases the diagnosis of recidivant cholesteatoma was the main indication for the secondary operation In 17 cases only continuing inflammation or disturbing scar formation requiring a reconstruction were the indication for the secondary operation which revealed a secondary cholesteatoma.

Main emphasis is paid to recidivant cholesteatoma, as it represents a process that will always grow further and as such is often an absolute indication for operative treatment. Thirty-three recidivant cholesteatomata were found among these secondary operations. Fourteen of these were considered to belong to the residual type, 12 to the recurrent or migration type and 7 to the iatrogenous type of cholesteatoma (Turner 1970) At the primary operation cholesteatoma was found in only 15 of 33 cases in 5 exact information is not available and in 13 only chronic inflammation without cholesteatoma was revealed by the primary operation. When the type of primary operation was analysed in this group of secondary cholesteatomata, it was shown that any type of middle ear operation may be followed by secondary cholesteatoma. The recurrent or migration type of cholesteatoma is most often

Table II *Comparison of results of tympanoplasty on 269 dry and 266 discharging ears assessed by the mean pre- and postoperative hearing the air–bone gap hearing gain, and TI*

	Preop. hearing	Postop. hearing	Hearing gain	Preop air–bone gap	Postop. TI	Success ( )
Dry	51.5	28.3	23.2	14.6	25 4	89
Discharging	50.9	36.7	14.7	23.0	33.3	69
Total series	51.2	33.0	19.0	19 1	29.3	79

radical cavities in 27% of the cases. However the mean hearing gain was most marked in old radical cavities (35 8 dB), least in sequelae to otitis (24 8 dB) In myringoplasty the mean hearing gain was 17.9 dB in type I tympanoplasty 21 0 dB in type II usually with interposition of the incus or cortical bone, 25 0 dB and in type III 24 1 dB in which we generally used as columella the incus as auto- or homograft as well as cortical bone. Type IV tympanoplasty was not performed on dry ears, in which a reconstruction of the middle ear to type III was always tried.

Discharging ears

All ears had had chronic discharge and could not be rendered dry by conservative measures. In 54 cases there was perforation of the pars flaccida, in the remaining cases of the tensa 133 ears had a large or total perforation. The pathology of the ossicular chain especially of the stapes, was considerably more severe than in the dry ears (Table I) The main object was to clear the ear In all 269 cases mastoidectomy was done, clearing all cells, removing the mucosa from the antrum and epitympanum, and removing the posterior osseous meatal wall. After radical removal of the cholesteatoma or granulations all ears had in the *same stage* tympanoplasty type I in 52, type II in 97 type III in 95 and type IV in only 22 cases. The cavity was obliterated by a bipartite, superiorly pedicled flap of the subcutis-muscles. The auditory canal was dilated.

The assessment of the results was as with dry ears. Prior to the operation 9% and after the operation 47% had *social hearing* An air–bone gap of 0–15 dB was closed in 37% of 0–30 dB in 77% of the cases. Prior to the operation 69% had an air–bone gap greater than 30 dB, the remainder 15–30 dB A *hearing gain* exceeding 10 dB was obtained in 66% of more than 20 dB in 32% 19% achieved a gain of 0–10 dB, 10% no gain, and 5% exacerbation of the hearing. Prior to the operation 16% had a *TI* of 30 dB or more after the operation 56% of the cases. The results were identical in cholesteatoma (130 cases) and in granulating otitis (72 cases). We were, therefore, not reserved in operating upon chronic granulating otitis and central perforation. The bony annulus (the bridge) was preserved and narrowed in 107 cases, removed in 159 The hearing gain was the same in both groups. Therefore, we do not plan to preserve the bridge at any price, especially if this decreases the chances of obtaining a dry ear Eight ears have had constant discharge since the operation. The others have been dry at the completion of the treatment and for the following 6 months. The first part of the material was seen an average of 2 years after the operation 93% had dry ears. The results were most favourable in dry ears (Table II)

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RESULTS OF TYMPANOPLASTY

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Abstract The results of tympanoplasty on 269 dry and on 266 ears with chronic discharge including mastoidectomy and tympanoplasty in the same stage, were assessed by different criteria and compared. The best results were obtained in dry ears, but those in discharging ears were not bad either If the ear is not rendered dry by conservative measures, we recommend mastoidectomy and tympanoplasty in the same stage rather than in two stages.

There is still a surprising paucity of analyses on the results of studying major series assessing the *entire* material from a given period of time. From 1964 to 1970 we performed 535 tympanoplasties, 269 on dry and 266 on discharging ears. All ears operated on during this period were treated by tympanoplasty with six exceptions in which radical operation was carried out for special reasons. The results were assessed according to several criteria 3–9 months after the operation, in the range 500–2 000 cps.

Dry ears

Most of the ears had previously been discharging 71 had been dry for 1–3 months, 76 for 3 months to 1 year and 122 for more than 1 year In 146 cases the perforation was large or total, in 50 there was no perforation, but mainly incudal dislocations and adhesive otitis. In 103 cases the ossicular chain was intact but as a rule with tympanosclerotic, fibrous or osseous fixation in the remaining cases defective (Table I) Often the appearance of the attic, antrum or aditus was checked. Myringoplasty was carried out in 37 cases, type I tympanoplasty in 70 type II in 116, and type III in 46.

Prior to the operation 7% and after the operation 67% had *social hearing* An *air bone* gap of 0–15 dB was obtained in 63% of 0–30 dB in 95% of the cases. Prior to the operation 75% of the cases had an air-bone gap exceeding 30 dB while 25% had 16–30 dB A *hearing gain* of more than 10 dB was achieved in 87% of more than 20 dB in 56 of the cases. Hearing did not deteriorate in any of the cases, but in 3% it did not improve. Prior to the operation 14% and after 71% had a *TI (threshold of intelligibility)* of 30 dB or better The results varied widely in the various disease conditions and depended highly upon the method of analysis. Thus, social hearing in sequelae to otitis was obtained in 82% in tympanosclerosis in 75% in adhesive otitis in 52% and in tympanoplasty on old

Table I *Pathology of the ossicular chain in 269 dry and 266 discharging ears*

	Dry	Discharging	Total
Intact	103	54	157
Lacking lenticular process	24	18	42
Lacking long process of the incus	88	134	222
Lacking long entire incus	15	47	6[illegible]
Lacking parts of the stapes	16	14	30
Lacking entire stapes	[illegible]	87	113
Lacking parts of the malleus	32	65	97
Lacking entire malleus	8	19	27
Dislocation, fracture	22	0	22

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ADVANTAGES AND DISADVANTAGES OF CLOSED AND OPEN TECHNIQUES IN CHOLESTEATOMA

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Abstract. One s aim even in cholesteatoma cases should be a closed technique—when this can be done without too great a risk.

The aim of treatment of a chronic ear is to arrive at a result that anatomically and physiologically is as close to the normal ear as possible In cases of non-cholesteatomatous chronic inflammation it is, in fact, actually possible to reach a result that is very near the ideal we seek to obtain. In cholesteatoma cases the problem is much more difficult. In these we have the following alternatives:

1 A small cholesteatoma-pocket, which is free and totally removable in such case it is ''le to use closed technique and obtain good hearing result.

2. In cases where the whole cholesteatoma cannot be successfully removed we can judge the situation in the following way If we use closed technique we take the risk of a recidive cholesteatoma. Is this dangerous? Apparently not if we have the patient under observation and she is prepared beforehand for a new impending operation. In order to solve the problem in this way the patient s consent must be obtained.

If we consider that the use of the closed method is impossible in a certain case, we should endeavour to obtain a dry ear with as good hearing as possible—an ear that implies no risk for the patient. A thorough operative eradication of all diseased structures, together with a proper antibiotic-chemotherapy combined with corticosteroids, usually results in cessation of the inflammation. In a dry ear cholesteatoma is also less active. Open mastoid cavities are to be avoided. There are several methods of filling these cavities.

The fistulas of the labyrinth are discussed by Professor H. C. Andersen. Such a fistula has a decisive influence upon the operative method in these cases. Generally these fistulas are left untouched—particularly if the other ear is deaf—and an open technique is resorted to. However experience has shown that a closed technique can be successfully used even in such cases.

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OPERATIVE TECHNIQUE IN MASTOID OBLITERATION

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Abstract. A meatally based postauricular musculo-periosteal flap is recommended for cavity obliteration. With preserved canal wall, it prevents spreading of infections to the mastoid cavity In cases with removed posterior bony wall, a new rigid wall is reconstructed using cortical bone chips and bone dust between fascia and musculo-periosteal flap

Simple mastoidectomy in its classical form consists of removal of the mastoid air cell system via a postauricular incision down to the dural and sigmoid sinus lamina and labyrinthine capsule, with preservation of the posterior bony ear canal wall. After healing, a deep postmastoidectomy depression can often be seen behind the ear while in some the mastoid cavity may become relined with endothelium and the depression may remain small.

During the 1950s we (Palva et al., 1959 1964) saw many cases of mastoiditis complicating acute otitis media. After mastoidectomy and healing, later otitic infections in some cases spread rapidly from the middle ear to involve also the area of the mastoid cavity To preclude such recurrent mastoiditis, I began to obliterate the mastoid antrum with a meatally based musculo-periosteal pedicle flap which was fixed over the antrum by gelatin sponge (Palva & Pulkkinen, 1959· Palva, 1962). This method proved effective in the prevention of recurrent mastoiditis and, in addition, minimized the size of the postauricular depression.

Having initially used temporal muscle fascia only for drum reconstruction, I began to use it together with this meatally based musculo-periosteal flap for ear canal reconstruction in radical ear surgery (Palva, 1962, 1963) Until then the creation of open radical mastoidectomy cavities was the routine method, and as there were often difficulties in postoperative treatment, my aim was to get rid of the cavity entirely Recently we have used, for posterior canal wall reconstruction, the soft tissues in combination with periosteum-containing large cortical bone chips, cemented in place with cortical bone dust. With this method a new bony posterior ear canal wall can be accomplished in 6–8 weeks.

The postauricular incision is made through the skin only which is then undermined posteriorly The musculo-periosteal flap can be tailored to a very big or smaller size depending upon the size of the expected cavity After cutting the flap superiorly posteriorly and inferiorly it is dissected free of bone but left attached to the meatus. The planum mastoideum and the ear canal are then exposed Cortical bone chips with some periosteum attached are removed with a broad chisel and stored in saline Using a large Stryker burr and continuous liberal irrigation with suction, the bone dust is then collected from the healthy dense cortical bone areas (Perkins, 1972). Ampicillin solution is added to the bone dust.

Having completed the mastoidectomy I proceed with swing door incisions in the soft ear canal wall and reflect the flaps superiorly and inferiorly (Palva et al., 1969). By this

method an excellent view into the middle ear and attic is obtained. If there is no cholesteatoma a small rim of the bony meatal wall is removed, as in stapedectomy to expose the incudo-stapedial joint. Working from both sides of the bridge, as suggested by Myers & Schlosser (1960), one can do a thorough clean-up The mastoid cavity is obliterated by the meatally based musculo-periosteal flap there being no need for canal wall reconstruction, as the wall is intact.

For elimination of attic cholesteatoma the posterior ear canal wall should only be removed partly leaving most of its inferior portion intact In cases with more extensive tympanic cholesteatoma most of the posterior ear canal wall must generally be removed. In these ears the anterior part of the fascia is used for drum repair the ear canal is filled with antiseptic gauze to retain its original size and the remaining major part of the fascia is lifted up to cover the posterior side of the ear canal skin Periosteum-containing cortical bone slices are then placed posterior to the fascia starting from the level of the horizontal canal up to the level of the cortical bone These broad bone chips are cemented in place by the bone dust. The musculo-periosteal flap is now placed into the cavity posterior to this bony reconstruction If necessary gelatin sponge artificial bone or more cortical bone chips and bone dust may be used to fill the possibly remaining cavity The tamponade can be removed from the ear canal in 6–7 days and the ear needs weekly checking for a period of 3–4 weeks. After this time the ear canal is well stabilized

In recent years much has been written on the preservation of the posterior bony ear canal wall and this seems to be the main object of the operation according to some reports. The canal wall can and should in practice be preserved in all cases of chronic otitis without cholesteatoma. In cases with small attic cholesteatoma, removal of the canal wall may be limited. However in cases with large cholesteatoma the first duty of the surgeon is to remove the cholesteatoma epithelium entirely and, in doing so he should not hesitate to remove as much of the posterior ear canal wall as is necessary for total eradication. The recurrence rate is high if the main emphasis is placed on posterior bony wall preservation, but remains low if the surgeon aims primarily to remove the disease Total removal of the bony posterior canal wall does not compromise the postoperative hearing level though the tympanic cavity may become slightly shallower than with preservation of an intact posterior wall.

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ONE STAGE VS. TWO-STAGE PROCEDURE FOR CHOLESTEATOMA

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Abstract The otosurgeon has to face the choice between a one-stage vs. a two-stage operation while eradicating a cholesteatoma. Referring to selected examples his considerations are discussed.

The operative treatment for chronic otitis unites the classic objective of *eradicating* a focus with the modern ambition to *stimulate* the hearing function. Such an achievement requires the elimination of complex pathological processes linked to such cell types as epithelium and connective tissue of skin and tympanic membrane, mucosal lining and osseous material of the temporal bone and ossicles. Chronic otitis also implies a physically abnormal milieu for sound transmission and protection within the tympanic cavity An imbalance exists between sound stimulation and the cochlea. Furthermore, one must bear in mind that an optimal middle ear function is related to the mastoid process and a patent Eustachian tube. Chronic otitis ends in cholesteatoma, osteitis, a change in the mucosal vitality and disproportion between its serous and mucous producing elements. Other effects of the infection are hyalinization, calcification or ossification. These are all factors to be dealt with, whether one applies an open or a closed technique, or if one realizes it during a one-stage or a two-stage operation.

For the sake of brevity we postulate that the eradication of the chronic process has been carried out two questions now arise (1) Using a conventional open technique, how far to go in a one stage operation only and how far to go provided the plan is to return for a second stage after say 6 months? (2) How is the challenge replied to by those using a closed technique like CAT? (combined approach tympanoplasty).

In the following, some simple examples are constructed and the decision to use 1 or 2 stages is weighed.

1 Preoperatively the chain is considered intact. A marginal perforation with cholesteatoma is recognized in the attic. The surgeon preferring an open technique decides to eradicate the process in the attic, and only eventually extend to a radical cavity but saving the bridge and hence preserving the suspension of both hammer and anvil. The defect in the membrane is closed with fascia. Thus the operation is completed in one stage. The CAT procedure includes a mastoidectomy and a dissection of the cholesteatoma out of the attic. It is all completed in one stage and the surgeon maintains that his method excludes the risk of establishing a postoperative retraction under the bridge. The hearing result should be the same.

2. A cholesteatoma is located in the attic and the antrum. The long process of the anvil is missing. Using a conventional open technique the surgeon completes in one stage but has to sacrifice the bridge. Optimal hearing is brought about while adapting fascia and/or the membrane to the stapedial head. The anvil may also be used as a link between the stapes

and the head of the hammer in a one-stage trial. Alternatively the cholesteatoma is removed in a first step, and when the soft tissues are consolidated above the oval window the surgeon returns for the second stage some 3–6 months later To ensure a maximum of sound energy transmission a lever system is constructed between stapes and the membrane. The CAT-surgeon may maintain that his one stage operation is the superior in saving the bony meatus wall, producing the best hearing and avoiding a persisting radical cavity

3 The cholesteatoma is spreading to the attic and the mastoid process. The anvil is missing and the stapes plate is left. Following an open technique the cholesteatoma is removed during the first stage checking the facial nerve and the windows. Care is taken not to dislodge the plate in the presence of infection. The mucosal lining appears abnormal and the Eustachian tube may be partially blocked. During this first stage no attempt is made to reconstruct any columella effect. The closing endeavour with a good fascial transplant prepares the basis for a future sterile tympanic cavity in which the second stage is performed later The surgeon who believes in a CAT procedure will do his operation in one stage, placing some kind of a columellar system on the plate His opponents will argue against an attempt to complete in one stage and strongly recommend the acoustic repair to follow in the second, for fear of damage to the stapes plate during the first healing period. In situations with tympano-sclerosis of the oval window however the CAT-surgeon will take no steps to eliminate the sclerosis as part of a one-stage operation. He is determined to leave such sclerosis untouched and to return for a second stage when the cavum tympani is deemed sterile.

4 The patient is under 10 years of age. Cholesteatoma is present and the hearing is very good. In children the expansive growth of cholesteatoma is rapid into the mastoid process, extending to the window niches. A good preoperative hearing is often maintained while the cholesteatoma acts as a false link. Recurrence is frequently encountered following both techniques, whether of 1 or 2 stages. The oval window niche is difficult to clear and so also is the tympanic and facial sinuses. The CAT-surgeon thoroughly eradicates the cholesteatoma in his first stage, avoiding any hazards in the stapes area. The restoration of hearing is postponed for the second operation when after a long observation no cholesteatoma recurrence is to be feared. When dealing with a child in a similar situation a two-stage operation is generally recommended. The consequence of an open method is the inconvenience of a radical cavity whereas the closed method has no drawbacks of this kind. Which method has the highest rate of recurrence? Apparently the closed one Which method gives the best hearing? The advantages of the closed way are notable. It is up to the surgeon to select a suitable procedure guided by the prevailing circumstances and aided by the components of the middle ear still serviceable By no means should a desire to solve all problems in one single stage be given priority when a two-stage operation is the safer in respect of preservation of the inner ear

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HISTOLOGICAL MALIGNANCY GRADING OF SQUAMOUS CELL CARCINOMA OF THE PALATE

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Abstract The histological point system grading of malignancy applied in the present study to squamous cell carcinoma of the palate gives a considerably more accurate measure of the ultimate prognosis than the earlier used system solely based upon an estimation of the degree of the differentiation of the tumours. It seems justified to consider this type of histological evaluation as an improved basis for the choice of therapy in individual cases.

The prognostic information which can be obtained from the histological differentiation of squamous cell carcinomas in highly and poorly differentiated tumours has been demonstrated by Eneroth et al. (1972) in a study of palate tumours (Table I). Thus, 51% of the patients with highly differentiated carcinomas died of the tumour disease, compared with 68% of the patients with poorly differentiated carcinomas. As was pointed out by Eneroth et al. (1972) the need for an improved morphological grading of malignancy is obvious.

Table I. *Squamous cell carcinomas of the palate: prognosis solely in relation to the degree of differentiation of the tumours*[a]

Histological features	No. of patients	Died of tumour disease n	%
Highly differentiated	75	38	51
Poorly differentiated	37	25	68

[a] From Eneroth et al., 1972.

Table II. *Histologic grading of malignancy based upon the tumour cell population*

	Points 1	2	3	4
Structure	Papillary and solid cords	Strands	Small cords and groups of cells	Marked cellular dissociation
Differentiation	Highly keratinization	Moderately some keratin.	Poorly minim. keratin.	Poorly no keratin.
Nuclear polymorphism	Few enlarged nuclei	Moderate number of enlarg. nuclei	Numerous irregul. enlarg. nuclei	Anapl. immature enlarg. nuclei
Mitoses	Single	Moderate number	Great number	Numerous

Table III *Histologic grading of malignancy based upon the tumour-host relationship*

	Points			
	1	2	3	4
Mode of invasion	Well defined borderline	Cords, less marked border line	Groups of cells; no distinct borderline	Diffuse growth
Stage of invasion	Possibly	Micro-carc. (few cords)	Nodular into connect. tissue	Massive
Vascular invasion	None	Possibly	Few obvious	Numerous
Cellular response (plasmolymphocytic)	Marked	Moderate	Slight	None

Therefore we have used a new system for the histological evaluation of the grade of malignancy in squamous cell carcinoma of the palate The system—also applied by us in evaluating the degree of malignancy of squamous cell carcinoma of the larynx (Jakobsson et al.)—is based upon a registering of 8 different morphological criteria in a 1–4 point scale giving total point values for the tumours from 8 to 32. In Table II is the tu mour cell population and in Table III the relation of the tumour to adjacent tissues registered according to the 1–4 point scale.

Table IV *Squamous cell carcinomas of the palate survival time for patients who died of tumour disease*

of patients		Time for death after treatment (within years)		
Total	Died of tumour	1	2	3
110	62	44	55	59

Table V *Squamous cell carcinomas of the palate prognosis based on histological grades of malignancy*

Grades of malignancy points	No. of patients	Died of tumour disease	
		n	
10–16	28	2	7
17–23	55	35	64
24–30	27	25	93
Total	110	62	56

Present series

In the present study we have applied this point scale system for grading the malignancy of 110 cases of squamous cell carcinomas of the palate which have been followed up for at least 5 years (5–40 years). The incidence of death in the tumour disease has been used as the criterium of prognosis.

The histological analyses were performed without any knowledge of the clinical stage, the treatment, or the further course of the disease.

The results are presented in Fig. 1 It is obvious from the figure that a fairly good cor relation exists between the histological grade of malignancy and the number of patients who died of the tumour disease Thus, few patients

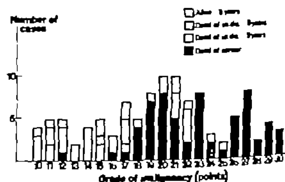


Fig 1 Histological malignancy grading of squamous cell carcinoma of the palate in relation to prognosis.

died of tumours receiving a low point value, whereas patients with tumours acquiring a high point count run a great risk of dying from their tumour disease independent of other factors such as clinical stage and therapy. As is also seen from the Fig. 1 a fairly large number of patients had died of intercurrent disease within or after 5 years of follow-up. However the great majority of the patients who died of intercurrent disease after 5 years must be considered cured of their tumour disease, since out of 62 patients who died from tumour disease only 3 died later than 3 years after treatment (Table IV).

In order to make a direct comparison possible between the prognosis which was previously based upon the degree of differentiation of the tumours (Table I) and the prognosis which can be estimated from the point system applied, the material has been divided into 3 groups, each with a 7 point interval. In Table V the result of this follow-up study is presented. Among patients with tumours acquiring a total point value between 10–16 only 7% have died from tumour disease. In the group with the high point value (24–30) no less than 93% of the patients have died of the tumour disease. The death rate from the tumour disease was also considerable in the intermediate group (17–23 points) 64% died from their tumours in this group.

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Table III *Histologic grading of malignancy based upon the tumour-host relationship*

	Points			
	1	2	3	4
Mode of invasion	Well defined borderline	Cords, less marked border line	Groups of cells; no distinct borderline	Diffuse growth
Stage of invasion	Possibly	Micro-carc. (few cords)	Nodular into connect. tissue	Massive
Vascular invasion	None	Possibly	Few obvious	Numerous
Cellular response (plasmolymphocytic)	Marked	Moderate	Slight	None

Therefore we have used a new system for the histological evaluation of the grade of malignancy in squamous cell carcinoma of the palate. The system—also applied by us in evaluating the degree of malignancy of squamous cell carcinoma of the larynx (Jakobsson et al.)—is based upon a registering of 8 different morphological criteria in a 1–4 point scale giving total point values for the tumours from 8 to 32. In Table II is the tumour cell population and in Table III the relation of the tumour to adjacent tissues registered according to the 1–4 point scale.

Table IV *Squamous cell carcinomas of the palate: survival time for patients who died of tumour disease*

No. of patients		Time for death after treatment (within years)		
Total	Died of tumour	1	2	3
110	62	44	55	59

Table V *Squamous cell carcinomas of the palate: prognosis based on histological grades of malignancy*

Grades of malignancy points	No. of patients	Died of tumour disease	
		n	
10–16	28	2	7
17–23	55	35	64
24–30	27	25	93
Total	110	62	56

Present series

In the present study we have applied this point scale system for grading the malignancy of 110 cases of squamous cell carcinomas of the palate, which have been followed up for at least 5 years (5–40 years). The incidence of death in the tumour disease has been used as the criterium of prognosis.

The histological analyses were performed without any knowledge of the clinical stage, the treatment, or the further course of the disease.

The results are presented in Fig 1. It is obvious from the figure that a fairly good correlation exists between the histological grade of malignancy and the number of patients who died of the tumour disease. Thus, few patients

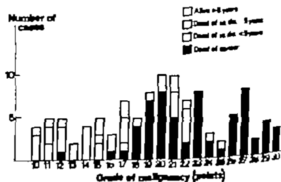


Fig 1 Histological malignancy grading of squamous cell carcinoma of the palate in relation to prognosis.

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NUCLEAR DNA CONTENT AS A CRITERION OF MALIGNANCY IN SALIVARY GLAND TUMOURS OF THE ORAL CAVITY

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Abstract Deviation from the normal number of chromosomes is a characteristic feature of most malignant tumours and they are often great enough to cause changes in the nuclear content of DNA detectable by means of quantitative cytochemical methods. In malignant tumours of the parotid gland we have found that the nuclear DNA content of these tumour cells, as determined by quantitative cytophotometry was increased by 25 to 50% above the normal value. It was therefore believed that cytophotometric DNA analysis could add further information as to the question of malignancy of salivary gland tumours where morphologic methods are uncertain. Regarding the tumours of the oral cavity the question of malignancy is still a matter of controversy in two types of tumour namely monomorphic adenoma and highly differentiated mucoepidermoid tumour The cytophotometric DNA analysis of the present study showed that the nuclei of the monomorphic adenomas had identical DNA values with the normal control cells. The highly differentiated mucoepidermoid tumour cells, on the other hand, exhibited higher DNA values, which were comparable with those of malignant parotid tumour cells. This adds further support to the idea that the monomorphic adenomas, despite the high cellularity are benign tumours, while the highly differentiated mucoepidermoid tumour should be considered as a malignant tumour

During the last two decades various histological features of salivary gland tumours have been correlated with the corresponding clinical course in such a large number of patients that it has been possible to classify well delimited types of tumours as benign or malignant.

There are, however two types of tumour in which the question of malignancy is still a matter of controversy namely monomorphic adenoma and the highly differentiated type of mucoepidermoid tumour

These two types are found mainly in the oral cavity where the relative incidence of mucoepidermoid tumour is about four times higher than in the major salivary glands (Eneroth, 1971). Monomorphic adenomas with a trabecular alveolar or tubular pattern are almost exclusively located in this region (Eneroth et al. 1972 *a*). The high cellularity and the frequent lack of encapsulation of monomorphic adenomas (Eneroth et al. 1972 *a*) are suspicious malignant morphological features. The morphologically benign structures, in cases with histologically highly differentiated mucoepidermoid tumour raise the question whether there is a benign variety of this type of tumour (Eneroth et al. 1972 *b*).

Increased nuclear DNA content is generally considered as a characteristic feature of most malignant tumour cells and therefore an analysis of the nuclear DNA content has been made in order to add further information on the question of malignancy of these two types of tumour

METHOD

After surgical removal of the tumours, imprint preparations were made and stained according to the Feulgen procedure. These

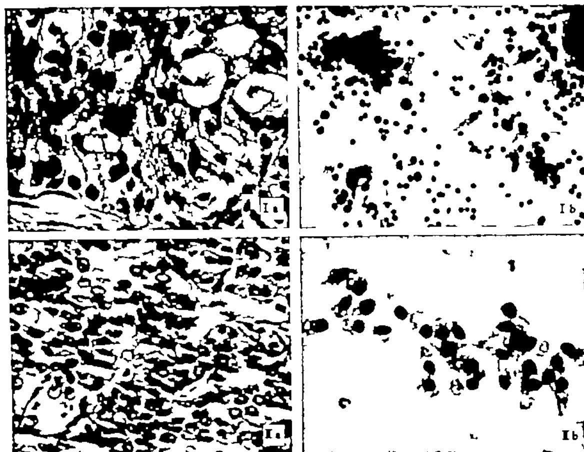


Fig 1 I. Monomorphic adenoma of the palate. (*a*) Histological features. Photomicrograph, ×245 (*b*) Imprints. Photomicrograph, ×245 II. Highly differentiated mucoepidermoid tumour of the palate. (*a*) Histological features. Photomicrograph, ×245 (*b*) Imprints. Photomicrograph, ×245

methods are described in detail elsewhere (Eneroth & Zetterberg, in press). Human lymphocytes from peripheral blood and cells from normal parotid glands were used as control cells. The DNA content of the Feulgen-stained individual cell nuclei was determined by absorption measurements in a rapid scanning microspectrophotometer (Lomakka, 1965) at the wavelength 546 nm. For the microscopic examination of the tumours routine histopathological techniques were employed.

RESULT

Fig. 1 shows the morphological pictures of a monomorphic adenoma and a highly differentiated mucoepidermoid tumour of the palate. The left part of the figure shows the haematoxylin-eosin stained sections of the tumours and the right part the haematoxylin eosin stained imprint preparations from the corresponding tumours.

Microspectrophotometric measurements of randomly selected Feulgen-stained nuclei of the imprint preparations are illustrated in Fig. 2. As control cells, human lymphocytes from peripheral blood were used. It is evident from the figure that the monomorphic adenoma cells contained the same amount of the nuclear DNA as the control cells (12-15 relative units). The mucoepidermoid tumour cells on the other hand, show a large inter-

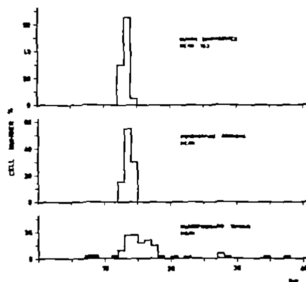


Fig 2 Intercellular distribution of nuclear DNA quantity (relative units, Feulgen-stained nuclei) in 75 human lymphocytes, 75 monomorphic adenoma cells and 75 highly differentiated mucoepidermoid tumour cells.

variation in nuclear DNA content from 7 to 38 relative units. It is important to point out that more than 50% of the analysed cells showed DNA values exceeding that of the monomorphic adenoma cells and control cells.

For purposes of comparison with a clearly malignant salivary gland tumour a DNA analysis was made of a low-differentiated adenocarcinoma of the parotid gland (Fig. 3). Both the mucoepidermoid tumour cells of the palate and the adenocarcinoma cells of the parotid gland show a similar increase and intercellular variability of nuclear DNA content, and both types of tumour cell populations differ greatly with respect to these DNA characteristics from the values of the normal parotid cell population.

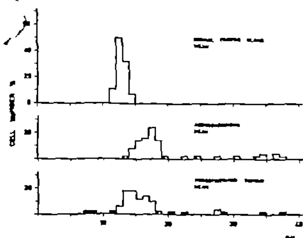


Fig 3 Intercellular distribution of nuclear DNA quantity (relative units, Feulgen-stained nuclei) in 75 normal parotid gland cells, 75 low-differentiated adenocarcinoma cells of the parotid gland and 75 highly differentiated mucoepidermoid tumour cells of the palate.

DISCUSSION

The cytophotometric DNA analysis in the present study shows that the nuclei of the monomorphic adenoma cells had DNA values identical with those of normal control cells. The highly differentiated mucoepidermoid tumour cells, on the other hand, exhibited higher DNA values, which were comparable to those of clearly malignant salivary gland tumour cells. Thus the DNA analyses of the present study indicate that the monomorphic adenomas, despite their high cellularity are benign tumours, while mucoepidermoid tumours with highly differentiated structures should be considered as malignant and therefore be denoted as carcinomas.

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SQUAMOUS CELL CARCINOMA OF THE GINGIVA

Histological Classification and Grading of Malignancy

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Abstract. The degree of histological activity in squamous cell carcinomas of the gingiva has generally been categorized by classifying the tumours as highly moderately or poorly differentiated. This classification has in the past been generally applied despite the rather heterogeneous morphology of these types of carcinoma. Thus, the tumours are frequently highly differentiated at the surface and less differentiated in the invasive, deeper portions. The correlation between the degree of tumour differentiation and the prognosis is of limited significance and this type of classification has proved inadequate as a basis for the choice of therapy in many cases. Consequently we have deemed it urgent to try to establish a more systematic histological classification for gingival carcinomas which better reflects the biological growth capacities of the tumours and might serve as an improved aid for therapy in individual cases.

At the Department of Tumour Pathology an attempt has recently been made to classify squamous cell carcinomas of the larynx according to new principles (Jakobsson et al. 1972). Such a modified classification has been applied by us on a 12 year material of squamous cell carcinomas of the gingiva, treated at the Department of Otolaryngology and Radiumhemmet, Karolinska Sjukhuset, during 1958–1969 (Nathanson et al., 1972) Altogether 125 cases have been investigated which comprise about one-third of all cases reported in Sweden during the same period.

The morphological analysis is based upon an evaluation of the *tumour cell population* in terms of a 1–4 point scale grading of the degree of differentiation the nuclear polymorphism, and the frequency of mitotic figures. Separately a corresponding grading is registered of the *tumour–host relationship* as measured by the mode and stage of invasion as well as the degree of lympho-plasmocytic infiltration, considered as a sign of the local immunological reaction. The 6 different morphological parameters can fairly easily be estimated in routine biopsies and require only a few histological sections. The morphological analysis, though aiming to be objective, involves certain subjective factors. The reproducibility of a single investigator has, however been high. All histological examinations have been performed without any knowledge of the clinical stage of the tumour the therapy or the subsequent clinical course of the disease.

The distribution of the individual cases according to the histological grade of malignancy expressed in terms of total points values, is demonstrated in Fig. 1 There is a tendency to a bionominal distribution with a group of low-point tumours to the left and another with high-point tumours to the right. It is also obvious that patients with metastasizing tumours fall exclusively within the high-point range. There is also an intermediate group of tumours with or without metastasis. Almost all patients with metastasizing tumours had their metastasis even on admission to

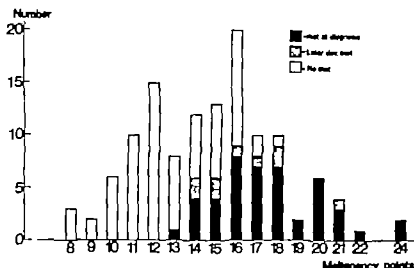


Fig 1 Histological grade of malignancy in 125 cases of squamous cell carcinoma of the gingiva, in relation to metastasis.

hospital (84%) Only a few developed metastasis later in the course of the disease (16%) This observation may suggest the presence of 2 principally different types of carcinoma, one fairly benign, which gives rise to metastasis either late or never and an aggressive, metastasizing form, analogous with what has been observed for cancer of the cervix uteri (Ashley 1966) No difference between the two groups of tumours was found in the average age of patients at onset of the disease The distribution of metastasis in relation to the number of patients in each group and the erent morphological parameters, showed, might be expected, more frequent metastasis from tumours with high-point values. The immunological response was mostly correlated to the type of tumour cell population whereas the mode of invasion specificallly paralleled the tendency to metastasis.

Dedifferentiation of the tumours during the course of the disease was rarely found in the material. Patients with multiple carcinomas in the oral cavity generally had a "finger print" response to the carcinogenic influence, reflected in a marked morphological resemblance between the different tumours.

The histological grading of malignancy presented thus implies a rather good correlation of the tendency of the tumours to metastasize. It would thus seem possible to forecast squamous cell carcinoma of the gingiva from tumour biopsies and thus make possible the institution of adequate therapy at an early stage of the disease.

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PROGNOSIS OF SQUAMOUS-CELL CARCINOMA OF THE GUMS

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Abstract The prognosis has been studied of 125 patients with squamous-cell carcinoma of the gums who were treated during the period 1958–1969 at the Karolinska Hospital. The material was classified according to the TNM-system (Geneva, 1968) and divided into 3 well-defined clinical stages. The determinate 5-year-survival rate was 73% in stage I (T_1–T_2), 41% in stage II (T_3–T_4) and 17% in stage III (patients with clinical metastases).

Carcinoma of the gums is a rare disease. Between 1959 and 1968, 358 new cases were registered in Sweden (Cancer Incidence in Sweden, 1959–1968) i.e., about 7% of all carcinomas of the mouth. Nevertheless, carcinoma of the gums is associated with many therapeutic problems, and opinions vary widely regarding treatment. The determinate 5-year-survival rate varies, according to the literature, between 19% (Mattick & Meehan, 1951) and 52% (Erich & Kragh, 1959) In patients with microscopically verified lymph-node metastases this figure has declined to 5% (Nathanson et al., 1971)

The aim of the present investigation was to study the prognosis of squamous-cell carcinoma of the gums in a material treated at the Department of Otolaryngology and Radiumhemmet, Karolinska Hospital, Stockholm.

MATERIAL AND METHOD

During the period 1958–1969 125 patients with histologically verified squamous-cell carcinoma of the gums were treated. Of these patients 81 were men and 44 women In 96% of all the patients cancer occurred after the age of 50.

The primary tumour was situated in the lower gum in 82 patients and in the upper gum in 43 The primary tumour was classified according to the TNM-system adopted by the International Union Against Cancer UICC, Geneva 1968. The material was divided into 3 clinical stages. Stage I consisted of T_1–T_2. 22 patients. Stage II consisted of T_3–T_4 54 patients, and stage III comprised all the patients with palpable regional lymph-nodes, regarded as containing metastatic growth ($N+$) 49 patients.

The observation period was 1 year for 125 patients, 3 years for 123 5 years for 110, and 10 years for 61

The primary treatment consisted of surgery in 20 patients, radiotherapy in 73 patients (12 patients received only palliative treatment) and 32 patients received radiotherapy and were also operated but combined treatment had been planned for only 14 of these patients. In 14 patients surgery consisted in a local excision in 26 patients radical neck dissection was performed, and in 8 patients only the submandibular glands were extirpated. Hemimandibulectomy was performed in 21 patients.

RESULT

The results of the primary treatment are shown in Fig. 1 where the material is divided accord-

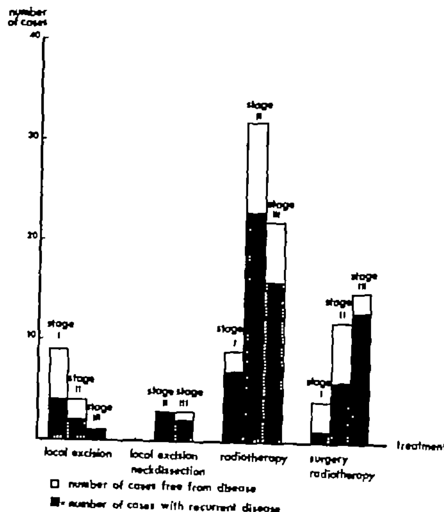


Fig 1 Results of primary treatment.

ing to the therapy given at the different stages. Here, all patients are excluded who were given palliative treatment. The best results were obtained with a local excision in stage I where 8 of 9 treated patients were still alive after 5 years, though 4 of these had a local recurrence, which was treated successfully by a new local excision. In stage II the determinate 5-year survival rate was 50% when surgery and radiotherapy were applied. In stage III the results were poor whatever form of therapy was given.

The determinate survival rate was calculated from the first histological verification of the tumour The comparative figures for the whole material, and the clinical stages are shown in Fig. 2. For all carcinomas the 5-year-determinate survival rate was 36% compared with 17% in stage III.

DISCUSSION

The results obtained in the present material support the findings in earlier materials (Martin, 1941) namely that the best results in the treatment of gingival carcinoma stage I are achieved with surgery alone. In one of 22 patients at this stage secondary metastases developed in our material. In stage II surgery and radiotherapy gave better results than surgery alone or radiotherapy alone This is in good agreement with the recently developed concept that a combined treatment is to be preferred in cases of advanced carcinoma of the oral

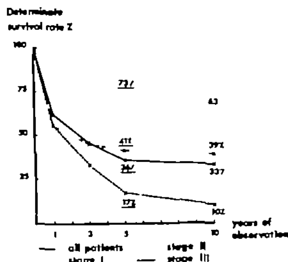


Fig 2 Survival of squamous-cell carcinoma of the gums treated 1958–1969 at the Karolinska Hospital.

cavity (Powers & Ogura, 1965). The poor results of surgery and radiotherapy in stage III is partly explained by the fact that many of these cases were not initially planned for combined therapy but were cases where radiotherapy had primarily given poor results, and surgery had then been applied, or inadequate surgery had been followed by postoperative radiotherapy Only 6 of the patients in stage III had tumours less than 2 cm in diameter The majority of the patients in stage III had extensive tumours with metastases, and were regarded as a poor prognostic group also in other materials (Cady & Catlin, 1969)

It seems probable that the metastasing tumours, with a comparatively early spread of tumour to the regional lymph-nodes, belong to an especially aggressive biological group and it is hoped that histological classification will give further information on these tumours where prognosis is especially poor

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REPAIR OF THE ORAL CAVITY AFTER IRRADIATION AND RESECTION FOR ORAL CARCINOMA

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Abstract Twenty patients with advanced carcinoma of the oral cavity were treated by major excisions of the oral cavity requiring procedures for reconstruction of the cavity walls. All patients had been treated with radiotherapy before operation. Operative procedures, postoperative complications, and results are discussed. The forehead flap was utilized in 10 cases, with very good results. The positive results support further work on combined radiotherapy and surgery in advanced cases of oral carcinoma, with use of reconstructive skin flaps when large defects are formed in the walls of the cavity

Combined treatment with radiotherapy and surgery of advanced carcinoma in the oral cavity has been proved to give better results than either surgery or radiotherapy alone (Fletcher & Jesse, 1962 Leonard et al., 1968) When high preoperative irradiation doses are given the rate of postoperative complications is considerably increased (Jakobsson et al., 1970 Bäckström et al., 1972) Introduction of well vascularized tissue at operation taken from areas located outside the irradiated field, will give better healing conditions and fewer complications postoperatively than surgical techniques using reconstructive procedures where only tissues from the irradiated area are utilized for reconstruction. Introduction of new tissue to cover large defects, especially in the floor of the mouth, will also reduce the post operative deformity considerably

The present paper deals with a follow-up study of 20 patients with advanced carcinoma of the oral cavity treated by major surgery in which the surgical defect was reconstructed with skin flaps. All patients had received irradiation before operation.

Six patients had squamous cell carcinoma of the buccal mucosa, 7 of the gingiva, 3 were sublingual and 3 located in the tonsils. One patient had a mucoepidermoid carcinoma of the buccal mucosa. Two patients had tumours classified as T_2N_0 according to the UICC classification, 8 as $T_3N_0M_0$, 2 as $T_3N_1M_0$, 5 as $T_4N_0M_0$ and 3 as $T_4N_1M_0$ (Table I)

Seven were planned combined treatment cases and operated on 1 to 4 weeks after radiotherapy Six cases were operated on after 2 to 6 months because of residual tumour and 2 cases respectively 9 and 10 months after radiotherapy Five cases were operated on for recurrent disease 3 to 11 years after radiotherapy (Fig 1)

The mean tumour dose was 5 400 rads, ranging from 2 000 to 9 000 rads, and administered for 14–71 days with 10–90 fractions. The irradiation was given with cobalt-60 teletherapy in 15 patients, with the short distance cobalt

Table I *Classification (UICC)*

No. of patients	20
T_2N_0	2
T_3N_0	8
T_3N_1	2
T_4N_0	5
T_4N_1	3

Supported by the Stockholm Cancer Society grant no. 71 72.

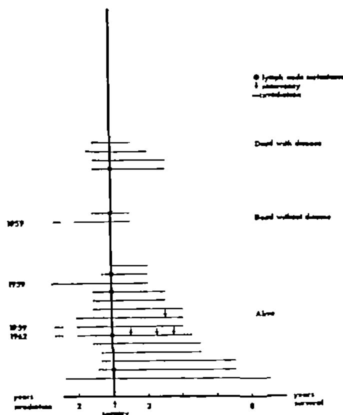


Fig. 1. Survival (in years) after surgery for extensive tumours of the one cavity

60 beam technique in 2 patients, with conventional roentgen therapy in 1 patient, with a 9 MeV electron beam in 1 patient and with a 6 MV linear accelerator in 1 patient. Five patients received 2 000–4 000 rads before operation. The majority of the group, 15 patients, received 4 500–9 000 rads (Table II).

In the earliest cases, the oral cavity defect was reconstructed using various methods, including local neck flaps, forehead flaps, Bakamjian flaps or acromiopectoral flaps. During the last 5 years we have more consistently used forehead flaps for inner lining of the oral cavity and local rotation flaps or Bakamjian flaps for replacement of large skin defects. Thus 10 patients had an oral lining with a forehead flap (McGregor 1963, Hoopes & Edgerton 1966), 5 patients with an acromiopectoral flap, and 1 patient with a Bakamjian flap (Bakamjian & Cramer 1960). In 4 cases

Table II

	Teletherapy (60_{Co} kilocurie)	Short distance technique (60_{Co} decacurie)	Linear accelerator (6 MV)	Electron beam (9 MeV)	Conventional roentgen
No. of patients	15	2	1	1	1
Mean dose	4 200 rad	6 600 rad	3 200 rad	5 400 rad	4 200 rad
Dose interval	(2 000–9 000) rad	(6 500–6 700) rad	—	—	—
Treatment	15–71	28–34	33	14	26
No. of fractions	10–90	24–25	22	12	22

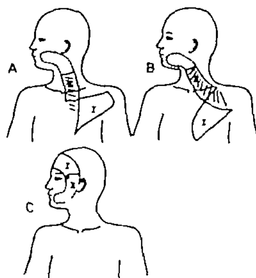


Fig 2 Schematic figure illustrating the rotation of flaps for covering of defects in the oral cavity The Bakamjian flap and the acromiopectoral flaps form a fistula on the neck which is closed secondarily The forehead flap is folded under the skin of the zygoma area and forms a fistula upward which is closed when the part of the flap not used for the covering of the defect in the oral cavity is put back on the forehead area. A. Bakamjian flap. B Acromiopectoral flap. C. Forehead flap.

rotation of a local flap from the neck was sufficient for inner lining (Figs. 2, 3 Table III).

Of 20 operated cases 12 had postoperative 1 with fistula formation (9) par flap necrosis (3) bone necrosis (1) or other necrosis (3) All complications healed either spontaneously or after further surgery and did not cause major distress for the patient (Table IV)

The patients were followed from 2 to 12 years postoperatively During the follow-up period 4 patients died of cancer 2 patients died without signs of cancer and 14 patients are alive more than 2 years after surgery with a mean survival time of 4.5 years. All patients

Table III. *Type of reconstruction*

Neck flap	4
Forehead flap	10
Acromiopectoral flap	5
Bakamjian flap	1

Table IV *Complications*

No of patients	12
Fistula	9
Partial flap necrosis	3
Bone necrosis	1
Skin necrosis	3

who died of cancer died within the first 4 years after surgery (Table V)

The results of treatment in this series of patients with advanced carcinoma of the oral cavity has been encouraging. We have demonstrated that major excisions of the oral cavity can be performed, and large defects reconstructed with skin flaps after radical doses of preoperative irradiation, without severe complications in the postoperative course. The use of forehead flaps or combinations of forehead flaps with other flaps decreases the fibrosis in the tissues of the oral cavity and the post operative problems with swallowing and eating. Introduction of well vascularized tissue from areas outside the irradiated field reduces complications after surgery does not increase operative risk, even in the elderly patient.

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Table V *Results*

No. of patients	20
Died of cancer	4
Dead of intercurrent disease	2
Alive	14
Mean survival time years	4.5

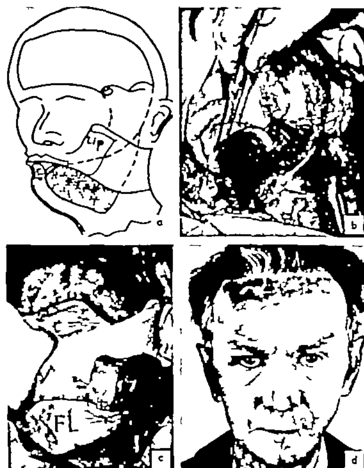


Fig 3 The forehead flap is wide enough to cover large parts of the floor of the mouth. *A* illustrates schematically the procedure used in covering of the large defect in the floor of the mouth formed when a large gingival carcinoma *T* was operated with resection of the mandible from the area of dens ¬ to the angle of the mandible of the left side with left side of the tongue and floor of the mouth. A radical neck dissection was made at the same time. *B* shows the defect. The tongue is held by forceps. *C* shows the forehead flap (Fl) in place before suturing down the flap including the lower lip which was cut in the midline (cf. A). *D* shows the patient 2 / years after operation.

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TOLUIDINE BLUE STAINING AS A MALIGNANCY TEST

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Abstract In order to get a reliable material at the cytological sampling or at the biopsy the Toluidine blue test has been designed. The method is based upon the fact that cancer cells contain quantitatively more DNA and RNA to which nucleic acids the Toluidine blue has an affinity For that reason an oral staining with that metachromatic dye delineates the region of malignancy of the epithelial mucosa. A consecutive study of 54 stained lesions was reported. The results were correlated to the histopathological investigations and proved to agree.

The reliability of the cytologic and the histopathologic diagnosis of cancer depends on the representativity of the tissue sent to the pathologic service.

The Toluidine blue test has been designed as a method to delineate the region of malignancy in a suspected lesion, which could hide ures essential to the pathologic investiga

The method is based upon the fact that cancer cells contain quantitatively more RNA and DNA. Toluidine blue has an affinity to these nucleic acids, and for that reason the malignant tissue will stain more strongly than will the normal epithelial tissue. At the Department of Oral and Jaw Diseases, Karolinska Hospital, this test has been utilized during the last 4 years. In this technique, factors which could weaken the reliability of the test were avoided.

The stain was used in a 1% water solution, the temperature of which was kept within a range of 15–20 degrees, and the pH value of the lesion was about 5

The lesions were cleaned and dehydrated in 1% acetic acid. The stain was applied abundantly to the lesion in question for 30 seconds. Decolourization was performed with 1% acetic acid. The staining results were then determined. If the lesions retained a deep blue or violet colour tone the test was considered positive.

A consecutive study of 54 lesions was performed. The results of the test were correlated to the histopathologic investigations of the same lesions and the results proved to agree. There was a small difference only in the dysplasia group The staining of the cancer cells was also studied by the technique of nitrogen-frozen sections (in collaboration with Dr Roger Willén, Department of Tumour Pathology Radiumhemmet, Stockholm). In this study the staining of malignant nuclear structures was remarkable.

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TONGUE CANCER

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The Cancer Registries of Finland, Iceland, Norway and Sweden have recently published a report on cancer incidence in these countries. According to these statistics Finland shows a decided male preponderance in total cancer incidence otherwise the differences between the four countries are small. The incidence of stomach cancer is very high in Iceland and also higher in Finland than in Norway and Sweden. On the other hand, the latter two countries have higher incidence of cancer of colon and rectum than Finland and Iceland. Sweden shows the highest rates in cancer of liver and biliary passages. The most striking feature in cancer of respiratory organs is the high male lung cancer incidence in Finland (more than 5-fold as compared with that in Iceland). On the other hand, in females Iceland has the highest rate, and the Finnish rate is equal to that of Sweden.

Table I. *Incidence of tongue cancer*

Incidence	Finland	Iceland	Norway	Sweden
Male	0.9	0.5	0.9	0.6
Female	0.6	0.8	0.4	0.4
Total	1.5	1.3	1.3	1.0

In laryngeal cancer too the Finnish male rate is high (3–4-fold as compared with that of the other countries) The Finnish rate for female breast cancer is only about two-thirds of the rates for the other countries. Carcinoma of skin is high in Finland. Iceland has a high rate of thyroid cancer

Table I shows the relative incidence of tongue cancer in Finland, Iceland, Norway and Sweden. The incidence rates are counted per 100 000 of population in Iceland 1957–66, in Finland, Norway and Sweden 1962–66.

The total incidence of tongue cancer is 50% higher in Finland than in Sweden. The rates for Iceland and Norway lie in between these two In Iceland the rate for women is higher than for men. In the other countries the order is the reverse.

The high incidence of tongue cancer in Finland may be related to dental caries and deficient hygiene of the mouth. Smoking habits are probably also an important factor

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CARCINOMA OF THE LIP

A Series of 869 Patients

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Abstract In a series of 869 patients with carcinoma of the lip the principles of treatment of the primary tumours and the regional lymph node metastases are discussed. The results of treatment are presented.

Between 1946 and 1966 a series of 869 patients with carcinoma of the lip were seen in the Radium Center and the E.N T Department in Aarhus.

The present report deals with the problems and the results of treatment of both the primary tumour and the metastases. 97.2% of the patients were males. As regards the age distribution the incidence was greatest in the group aged 60–69 All cases were squamous-cell rcinomas, 6 of these were basocellular car omas. A rather large number of the patients 57%) had the primary lesion for more than 4 months. In only 1.8% (16/869) of the patients was the tumour located on the upper lip The series was grouped according to the TNM classification in the UICC modification. There was a great preponderance of early cases, only 83 patients being *T3* and *T4* cases. In 14 patients regional lymph node metastases were found on admission. None of the patients had distant metastases.

The principles of treatment of the primary tumour can be seen in Table I

165 recurrences, residual tumours and new tumours occurred in 132 patients. In only 7 patients was it impossible to control the primary local tumour In a little more than half of the patients, secondary treatment was radiotherapy the rest underwent various operations.

The Radium-needle intubation failed in only 11% of the cases, but if the intubated *T3* cases are regarded selectively the recurrence rate was found to be 25% Therefore, the *T3* cases ought not to be treated by intubation. Because it is possible to control the primary tumour in the majority of the patients the malignant character of the carcinoma of the lips is determined by the tendency to metastases.

The incidence of the regional lymph node metastases in this series can be seen in Table II.

Most of the metastases were located in the submental or submandibular lymph nodes and no metastases jumped those primary lymph node stations.

TREATMENT

The results of treatment can be seen in Table III.

The two groups in Table III are not comparable. In the irradiation-group relatively

Table I

Intubation (10 mg radium needles)	766
External radiation	74
Operation	29
Total	869

Table II

Total no. of cases	Nodes present on admission	Node *involvement* at subsequent follow-up	*Total node* involvement at any time	No node involvement at any time
869	14 (1.6 %)	45 (5.2 %)	59 (6.8 %)	810

Table III

	No of cases	Dead from cancer labii	Dead from intercurrent disease	Crude 5-year survival rates
Neck dissection	37	9	3	68 % (25/37)
Irradiation	22	16	1	23 „ (5/22)*
Total	59	25	4	51 % (30/59)

* One patient alive at 5-year limit with recurrence.

more of the metastases were fixed than in the group of surgical treatment. The cases with histologically verified metastases in the surgical group had a 5-year crude survival rate of 56% (15/27). Fifteen patients in the surgical group had only partial neck dissections, and recurrences were seen in 9 of those patients. In 4 of these 9 patients the regional metastases were controlled by total neck dissections. There is reason to believe that total neck dissection as the initial attempt at treatment might have reduced the recurrence rate

Prophylactic neck dissection was not performed. However an analysis of the *T3*-cases showed that *T3*-cases with recurrence of the primary tumour of the lip had a frequency of lymph node metastases of 38% Therefore a prophylactic exploration of the submental and the submandibular lymph nodes should be considered in this special group. If freezing microscopy proves malignancy in the nodes a total radical neck dissection should be performed.

Five-year crude survival rate of the whole series was 84.5 ± 2.5% After correction for mortality from other causes than cancer the 5-year survival rate was found to be 96.7% i.e. only between 3 and 4% of the patients die from carcinoma of the lip.

In Fig. 1 the survival corrected curves for the *T1* *T2* and *T3* cases are shown.

Thus, most cancer deaths are found in the *T3* group, as mentioned, not because of the primary tumour in itself but because of a greater frequency of lymph node metastases.

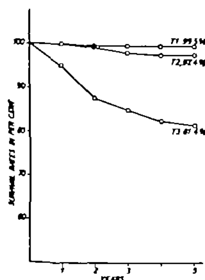


Fig 1

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treatment. The treatment established against the recurrences was dependent on the initial therapy and could be surgical or radiotherapeutical alone or in combination. A very few patients received chemotherapy or no therapy at all.

The 5-year survival rate of the total material was 45% (43 patients) with the following distribution in the different groups according to the TNM system.

T1	*T2*	*T3*	*T4*
14 (64%)	11 (46%)	10 (42%)	8 (32%)

No difference was found between males and females. Furthermore, 7 patients died of intercurrent diseases within 5 years without signs of malignant tumour.

In spite of the small material analysed here we wish to stress a few factors which might be of importance in raising the percentage of 5-year survivals.

1. All patients with cancer of the tongue irrespective of its grade should be treated surgically. A combined therapy surgical plus radiotherapeutical, could also be performed. The size of the surgical intervention should at least be partial glossectomy and a homolateral neck and submandibular dissection. In most cases a contralateral submandibular dissection must be considered, especially when the tumour is located near the midline of the tongue.

2. In patients with tumours above *T2* and in all patients with palpable nodes in the submandibular region a partial mandibular resection should also be done.

3. Where resection of the mandible has been performed, a space-occupying construction or transplant ought to be discussed. We think this is an important procedure in the postoperative rehabilitation of the patient.

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STROMAL REACTIONS AS PROGNOSTIC FACTORS IN EPIDERMOID CARCINOMA OF THE TONGUE

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Abstract The appearance and clinical significance of round cells and acid mucosubstances in the tumour stroma were investigated in 80 patients with epidermoid carcinoma of the tongue. It was found that on the average the prognosis was better in the cases where the round cell reaction in the tumour stroma was positive, and also in the cases where the acid mucosubstance reaction was negative in the tumour stroma. Furthermore, an inverse correlation between the appearance of round cells and acid mucosubstances was noted.

A malignant epithelial neoplasm forms a functional whole with the surrounding mesenchymal tissue. Obviously the clinical characteristics of the carcinoma depend on both the parenchyma and the stroma. In the earlier literature opinions differed as to the significance of the round cell reaction of the stroma for the prognosis of the patient. Most recent authors have found that a strong round cell reaction is often connected with a better prognosis (Hayashi et al., 1964)

Differing amounts of acid mucosubstances have been found in the stroma of malignant neoplasms. According to a recent investigation there is an inverse correlation between the appearance of mucosubstances in the stroma and the prognosis of the patient (Paavolainen, 1970)

No mucosubstance investigations have been made on neoplasms in the oral cavity In the present investigation the appearance as well as the significance of both acid mucosubstances and round cells have been investigated in parallel in a material comprising 80 epidermoid carcinomas of the tongue

MATERIAL AND METHOD

The material comprises 35 men and 45 women suffering from epidermoid carcinoma of the tongue. The mean age of the patients was 69.5 years. Some of the patients were subjected to radiotherapy alone, some to surgery alone, and some of the patients to both modes of treatment. The follow-up period was 5 years. The prognosis was estimated on the basis of the survival of the patients.

The round cell reaction was studied using the Weigert van Gieson staining method. The mucosubstances were stained with Hale's Colloidal Iron method.

RESULT

The following table (Table I) presents the correlation between round cell reaction and prognosis.

It is evident from the table that on the average patients with positive round cell reaction had a better prognosis.

Table II shows the correlation between acid mucosubstances and prognosis.

It can be seen that on the average the prognosis was better with patients with negative mucosubstance reaction.

Table I. *Survival by occurrence of round cell reaction*

Round cell reaction	No. of cases	Survival	
		No. of cases	
Absent	32	8	25
Present	48	20	4.
Total	80	28	

The following table (Table III) presents the correlation between appearance of both round cells and acid mucosubstances.

It is evident from this table that in the group where there was no mucosubstance reaction, the round cell reaction was clearly more often positive as compared with the group with positive mucosubstance reaction. In other words, acid mucosubstances and round cells seem to avoid each other's vicinity

DISCUSSION

The number of patients is so small that statistical conclusions are difficult to make. However these results agree with those obtained in a large laryngeal carcinoma material at our clinic (Paavolainen, 1970).

One possible interpretation of the results of the present investigation is the following: the mucosubstance coat surrounding the carcinoma acts as a barrier which prevents the cell-bound immunity influence on the tumour. Thus carcinomas which lack this barrier can more easily be destroyed by the organism itself. The theory presented by Currie & Bagshawe (1967) and

Table II. *Survival by occurrence of acid mucosubstances*

Mucosubstances	No. of cases	Survival	
		No. of cases	%
Absent	25	11	44
Present	55	17	31
Total	80	28	

Table III. *Number and percentage distribution of cases by round cell reaction and occurrence of acid mucosubstances*

Round cell reaction	Occurrence of mucosubstances			
	Absent		Present	
	No. of cases		No. of cases	
Absent	5	20	27	49
Present	20	80	28	51
Total	25	100	55	100

Kirby & Wood (1967) gives an interesting background for the interpretation of the results. It has been found that acid mucosubstances appear except around carcinomas also on the surface of the trophoblasts of the placenta. Carcinomas and embryos are the only foreign bodies" that the organism cannot effectively reject. As is known, carcinoma and embryo cells are morphologically similar to each other. On the other hand, some specific antigens are known to occur both in embryonic tissue and in carcinoma cells. It might be that the organism is not able to distinguish between a carcinoma and an embryo and thus begins to protect the carcinoma as the embryo by means of mucosubstances against its own mechanisms of rejection.

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TREATMENT OF SQUAMOUS CELL CARCINOMAS IN HEAD AND NECK WITH BLEOMYCIN AND WITH COMBINED BLEOMYCIN AND X-RAYS

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Abstract. The choice of therapy for patients with squamous cell carcinoma will depend of the histology of the tumour its extent and localization. X-rays and surgery alone and combined, are well established methods by which elimination of the tumour may be achieved. With a new therapeutical approach, combining bleomycin and X-rays, a possible synergistic effect has been obtained. It has in itself given surprisingly good results and when used as a preoperative treatment it offers possibilities of making an increased number of otherwise inoperable cases surgically accessible.

Bleomycin has been shown to have a significant therapeutic effect on squamous cell carcinomas, particularly those of the highly differentiated type. In contrast to other cytostatics it does not affect the bone marrow nor has it an immunosuppressive effect.

At the Department of Otolaryngology of Rikshospitalet, bleomycin has been used in about 100 cases of squamous cell carcinoma of the head and neck. To begin with we administered the usual dosage pattern of 30 mg i.v twice per week for 5–6 weeks. Based on animal experiments (Juul Jørgensen, 1971) and our own clinical observations we changed, 6 months ago to a combination treatment. bleomycin and X-ray

Before going any deeper into this new approach, we should report our experience with respect to the therapeutical efficacy and side-effects with bleomycin alone (Tables I, II).

One of the remarkable cases is a recurrent laryngeal carcinoma after radiotherapy Following the bleomycin treatment this tumour disappeared completely now $2\,^1/_2$ years ago. We would also like to mention 8 cases of carcinoma of the oral cavity and tongue which showed a profound regression. A tumour regression $>50\%$ often made it possible to remove the remainder by surgery In our experience bleomycin s most important field is presurgical chemotherapy

The surgery should be performed shortly (2–3 weeks) after the bleomycin treatment is completed.

The side-effect to cause most concern has been an interstitial pneumonia. We had only 2 cases, both with moderate symptoms. We cannot account for this apparent difference between our and others experience. A point of possible importance is to keep a slow rate of i.v injection.

We have seen no indications of damage to the inner ear

Experiments in mice with i.m. inoculated methylcholanthrene induced epithelial carcinomas. Juul Jørgensen (1971) has shown that simultaneous combination of bleomycin and X rays has significantly increased the therapeutical efficacy of the treatment. On the background of this study and our own experience with bleomycin as well, we have

Table I. *Response of tumour to bleomycin treatment in patients with squamous cell carcinoma*

Localization	No. of patients	Regression of tumour Complete	>50%	<50	None
Larynx	15	1		13	1
Oral cavity	8		4	3	1
Tongue	8		4	4	
Hypopharynx/oesophagus	5		1	4	
Epipharynx	1		1		
Nose/Sinuses	3		2	1	
Ear/Temporal bone	4		2	2	
Lacrymal sac/Orbit	1		1		
Skin (ext. ear)	2	1	1		
Lung metastases	1				1
Total	48	2	16	27	3

since November 1971 combined bleomycin with X-ray treatment.

Our schedule was as follows.

First week. Bleomycin i.m. 15 mg daily Mon.–Sat., given 1 hour before X-rays. X-rays, 350 R daily Mon.–Sat.

Second week. Bleomycin i.m. 15 mg Mon., Wed., Fri.

Third week. Bleomycin i.m. 15 mg daily Mon., Wed., Fri. given 1 hour before X-rays. X-rays, 350 R daily Mon.–Sat.

Total dosage: Bleomycin 180 mg. X-rays, 4 200 R.

The therapeutical response is shown in Table III.

Carcinoma of the oral cavity and tongue constitutes a relatively small group, but the results are very good. In the group of inoperable neck metastases complete regression was obtained in 6 cases and more than 50% regression in 3 cases. A total of 26 complete

Table III. *Squamous cell carcinomas response of tumours to combined treatment with bleomycin and X-rays*

Localization	No. of patients	Regression of tumour Complete	>50	<50	None
Larynx	17	11	5	1	
Oral cavity	2	2			
Tongue	2	1		1	
Hypopharynx/oesophagus	5	1	3	1	
Epipharynx	2	1	1		
Nose/Sinuses	5	2	2	1	
Ear/Temporal bone	2		1	1	
Parotid gland	1	1			
Skin (ext. ear)	1	1			
Inoperable neck metastases (laryngeal 7 cases) (tonsillar 2 cases)	9	6	3		
Total	46	26	15	5	

regressions out of 46 cases is also remarkable. Whether the effect of the combination treatment is synergistic or cumulative is difficult to decide. In patients with previously untreated tumour we have observed a conspicuously rapid regression. This fact and the results in patients with inoperable metastases in the neck, strongly indicate synergism. We must emphasize, however that these are only early results.

The side-effects we observed with the combination treatment are essentially the same as the typical side-effects for bleomycin alone and X-rays alone.

During the study of biopsies from bleo-

Table II. *Treatment with bleomycin side effects*

No. of patients	Swelling of skin	Stomatitis	Hair loss	Fever	Pruritus Erythema Pigmentation	Pulmonary lesions
56	38	29	20	7	6	1

Treatment stopped owing to skin lesions (toxicoderma): 5 cases.
Treatment stopped owing to stomatitis: 1 case.

mycin-treated patients, we have observed changes that may be of great significance. Islands of tumour cells are found where undifferentiated "basal-cell-like" tumour cells are no longer visible Such "Basal-cell-like" cells are ordinarily observed in untreated squamous cell carcinomas, and in squamous cell carcinomas treated with other cytostatics or with irradiation alone. In bleomycin-treated patients, where a good clinical effect is seen islands of cells are found that seem to have undergone maturation very rapidly Some of the nuclei have not lost their stainability and histology shows streaks of keratin or keratin-like substances with pycnotic nuclei similar to what in psoriasis is called parakeratosis. Around such islands of keratin are often found multinucleated giant cells of the foreign body type. Very few lymphocytes are seen. This may be interpreted as showing that bleomycin, in addition to its effect on cell proliferation probably also affects the keratinization process and speeds it up or changes it qualitatively This may be the reason why bleomycin has such good effect on squamous cell carcinomas, especially the highly differentiated types.

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COMBINED RADIOTHERAPY AND SURGERY IN TREATMENT OF CARCINOMA OF THE TONGUE

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Abstract. Twenty-three patients with carcinoma of the tongue were treated with combined radiotherapy and surgery. A follow-up study was made, demonstrating a 55% three-year determinate survival rate and a 43% five-year determinate survival rate. Postoperative complications were found only in patients treated preoperatively with more than 4 500 rads.

The variation in stages, location, and mode of therapy of carcinoma of the tongue makes it difficult to compare treatment results in various series. It is quite obvious, however, that there has been an improvement in treatment results during recent decades. The 5 year determinate survival rate for treatment of all cases of cancer of the tongue and floor of mouth lies around 40% whether surgery or radiotherapy is used (Harold, 1969; Montana et al., 1969). The cure rate falls rapidly from about 80% in small lesions of the anterior part of the tongue without metastasis, to less than 15% in large posterior tongue lesions with metastasis.

The aim of the combined use of radiotherapy and surgery is to reduce the tumour volume preoperatively by destroying the largest possible part of the tumour cell population and thereby increasing the chances for radical extirpation of the tumour. A decreased risk of spreading tumour cells or reinplanting the tumour during operation is also aimed at. Few controlled series with treatment results have, however, been published. A plea for collaborate studies in preoperative radiation was made by the editor of the Journal de l'Association Canadienne des Radiologists in 1965.

The increased risk of postoperative complications has been an obstacle which has made many surgeons unwilling to operate after irradiation. Refined techniques in radiotherapy as well as in surgery have, however, considerably reduced the risk of postoperative complications. In a recent publication Bäckström et al. (1972) demonstrated that there was no increase in postoperative complications, as compared with non-irradiated material, when the preoperative radiation dose was 4 000 rads or less, and given as a fractionated treatment over a period of 21 days.

Combined radiotherapy and surgery has been used consistently for the treatment of all cases of advanced carcinoma of the tongue treated at the Karolinska Sjukhuset during the last 5 years, and for selected cases during more than 10 years. All patients were seen by a joint group of radiotherapists and surgeons.

A follow-up study was made of 23 cases of carcinoma of the tongue treated during the years 1961 to 1970. The tumours were classified according to the UICC classification. Nineteen of the patients had advanced carcinomas classified as T_3 or T_4, and 4 were classified as T_1 or T_2. Six patients had cytologically verified metastases in the neck prior to treatment.

All patients received preoperative radiotherapy. The mean tumour dose was 4 400 rads (range: 2 800–6 700 rads) which was administered over 12 to 56 days, using 10 to 43 fractions. The irradiation was given with cobalt-60 teletherapy in 21 patients and with short dis-

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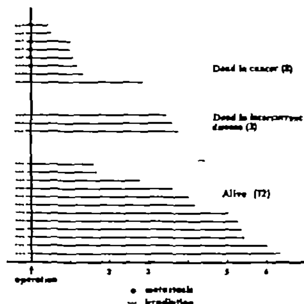
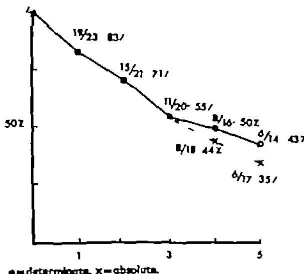


Fig 1 Survival (in years) after combined therapy for cancer linguae.

tance cobalt-60 beam technique in 2 patients. All patients were operated upon within 3 months of completion of radiotherapy In 16 patients the operation consisted of partial excision of the tongue and neck dissection on one side. Seven patients had a partial excision of the tongue only

The follow-up period varied between 2 and 11 years (mean 5 8 years)

Eight patients died of cancer during the observation period (Fig. 1) Three patients died of intercurrent disease and 12 are alive. The 3 year determinate and absolute survival rate was 55% The 5 year determinate survival rate was 43% and the absolute survival rate was 35% (Fig. 2)



●=determinate. x=absolute.

Fig 2 Survival, expressed as a percentage and in number of years after treatment.

None of the 14 patients treated with 4 500 rads or less had any postoperative complications. Nine of these are alive without tumour 4 died of cancer less than 2 years after operation, and one died of intercurrent disease 4 years after treatment. Among the 9 cases that received doses higher than 4 500 rads there were 2 with some necrosis of the oral mucosa, one with a cutaneous fistula, and one patient had difficulty in swallowing during the first month The fistula healed without operation. Five of these patients survived more than 3 years without cancer All of these patients carried on a normal life less than 4 months after operation. Two of the 5 patients died of intercurrent disease 3 1/2 years after operation.

In conclusion, we feel that a radiation dose of 4 000 rads or less given over 21 days to the oral cavity does not increase the risk of postoperative complications and is well tolerated by the patient. The treatment results are promising and support further work along the same line. We are convinced that preoperative radiotherapy is a valuable adjunct to surgery in the treatment of advanced carcinoma of the tongue.

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BLEOMYCIN THERAPY AND OTOTOXICITY

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Abstract *Bleomycin* produced regression of tumours in 10 of 15 cases of human squamous cell carcinoma. Hearing and equilibrium were not affected. No ototoxic effects were found in guinea pigs when Bleomycin was administered subcutaneously and intraperitoneally Cochlear damage was seen when the drug was injected into the middle ear

Fifteen cases of squamous cell carcinoma were treated with an average total dose of 300 mg of Bleomycin. Results of this treatment are shown in Table I.

Good tumour regression was observed in 3 of the cases. In one of these remission has lasted for over a year In 5 of the cases lung complications occurred, one of them being fatal. Other side effects noted were nausea, skin and mucosal lesions, hair loss, and fever In 2 cases acute bleeding gastric ulcers occurred during treatment.

In 6 controlled cases, vestibular function and hearing were found to be unimpaired by the treatment.

Since some antitumour agents such as nitrogen mustard in high concentration have been shown to be ototoxic (Cummings, 1968) and since Bleomycin is an antibiotic of the glucosamide group (Umezawa et al. 1966, Ishizuka et al., 1967), some members of which have serious ototoxic effects (Kohonen, 1965), an experimental investigation was conducted into the ototoxicity of Bleomycin. Three groups of guinea pigs were exposed to the drug by different routes of administration [illegible] and 2 received 35–40 mg sub[illegible] intraperitoneally respectively [illegible] of 1 week. Group 3 received [illegible] 1–2 mg in 0.1 ml saline [illegible] the tympanic membrane [illegible] and 2 which had received a [illegible] ten times greater than [illegible] cancer therapy showed [illegible] phological ototoxic effects [illegible] surface specimen tech[illegible] 1966) supplemented by [illegible] scopy Animals in Group 3 [illegible] hair cell losses when [illegible] than 1 week after treatment [illegible] vestigation showed th[illegible] and/or shorter survival times [illegible] hair cell losses. Larger doses [illegible] earlier and more severe damage [illegible] hair cells were damaged before second and third row outer hair cells. Inner hair cells did not appear to be damaged. Damage was most pronounced at the base of the cochlea and decreased toward the apex. Similar effects have been reported as a characteristic of some antibiotics (Kohonen, 1965).

Peroxidase-benzidine staining was used [illegible] investigate the effect of Bleomycin on the stria vascularis. Group 1 and 2 animals [illegible] no effects. In the animals of Group [illegible] general atrophy of the stria [illegible] observed. In one of the Group [illegible]



Fig 1 Hair cell damage in the organ of Corti of a guinea pig after injection of Bleomycin into the middle ear The scanning electron micrograph (A) reveals that all three rows of outer hair cells are affected. The phase contrast micrograph (B) emphasizes the sensitivity of the cells in the first row (*arrow*).

circumscript lesion characterized by sharp interruption of several stria capillaries and the formation of fibrous capillary strands, was found in the third coil. Further investigation is required to *determine* if this lesion represented an effect of the *Bleomycin* or had some other etiology

CONCLUSION

…omycin which appears to have some value …an antitumour agent in humans, was *found* to have no ototoxic effect on guinea pigs when administered in the normal parenteral way in doses per weight unit far *exceeding those* used in human antitumour therapy However hair cell losses were found in guinea pig cochleas when the drug was injected through the tympanic membrane.

Table 1 *Effect of Bleomycin in 15 cases of squamous cell carcinoma*

Localization	No. of patients	Regression of tumour			
		Complete	>50	<50	None
Tongue	5	—	1	2	2
Oral cavity	2	—	1	—	1
Nasopharynx	2	—	1	1	—
Hypopharynx	3	—	—	1	2
External auditory canal	[illegible]	—	—	2	—
Skin	1	—	—	1	—
Total	15	0	3	7	5

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AUDIOLOGICAL AND MORPHOLOGICAL ASSESSMENT OF EFFECT OF NOISE ON COCHLEA AND BRAIN STEM IN CAT

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Part 1 *Audiological Assessment* (G Lidén)

The pathogenesis of the loudness recruitment phenomenon has long been of considerable interest. There are few clinical reports on this matter based on autopsy observations. The purpose of this experimental study on cats was to correlate noise-induced hearing loss and recruitment to underlying structural changes in the cochlea and in the brain stem.

Eleven unilaterally labyrinthectomized cats were exposed to broad band noise of 115 dB SPL continuously for 8 hours. The tone thresholds before, immediately after and finally 3 1/2 months after exposure were determined with avoidance conditioning technique.

Recruitment of loudness was considered to be present in the cat with induced hearing loss if the stapedial reflex could be elicited at the same level as before exposure. The reflex was elicited by means of sound stimulation in the same ear in which the reflex was measured, in accordance with the method given by Møller 1960.

The results showed an average hearing loss of 45 dB in the frequency range 500-2 000 Hz. The induced loss did not change the thresholds of the stapedial reflex, thus indicating the presence of loudness recruitment. The details of the audiological part of this study has been published elsewhere (Lidén 1970).

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Part 2. *Effect on Inner Ear Sensory Cells* (H. Engström)

The structural modifications resulting from noise exposure have been studied by the surface specimen technique (Engström et al., 1966) and in a few cases also by scanning electron microscopy (Engström & Engström, 1972).

RESULT

In all animals except one (LL 27) we have made a practically complete preparation of the organ of Corti and recorded the presence or absence of almost all outer and inner hair cells. In spite of the pronounced loss of hearing as recorded above the extent of hair cell loss is rather small. In the first and second row of outer hair cells the percentage of lost cells is less than 2% while the third row has a somewhat more pronounced sensory cell loss. In certain areas this cellular destruction is more pronounced but in no animal is there a

complete loss of sensory cells such as we have often found after exposure to impulse noise (Bredberg et al., 1972)

DISCUSSION

In this series of unilaterally "labyrinthectomized" cats exposure to noise has caused a considerable hearing loss, as found by audiometric examination (avoidance technique). This hearing loss is paralleled by a morphological modification of the organ of Corti with loss of sensory cells, especially in the third or outer most row of hair cells. The loss is less extensive than expected and this is in good agreement with the results of several recent observers (cf Hunter Duvar 1973) indicating that a considerable hearing loss may be found in spite of a moderate loss of sensory cells. This indicates that functional modifications causing hearing loss may appear inside the organ of Corti while most hair cells are still present. Studies under the scanning electron microscope indicate that small modifications, difficult to observe by light microscopy may be found with improved technique. A fuller report on these studies will be reported elsewhere.

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Part 3 *Effect on Cochlear Nuclei of Brain Stem* (J G Hall)

The histological examination of the material was undertaken in order to find (1) whether the experimental lesions have produced degenerative changes in the neurons of the nuclei, and (2) if any loss of neurons demonstrable in these nuclei.

The total number of cells was computed in 10 of the cases according to the method described elsewhere (Hall, 1964) For controls, 6 normal adult cats were also counted.

Two main types of neuronal changes were observed. One type was characterized by shrinkage of the perikaryon and pycnosis of the nucleus. The other type was distinguished by chromatolysis. Both types of degeneration occurred bilaterally on the labyrinthectomized

Table I *Cell counts*

R = Right side, noise-exposed L = Left side, labyrinthectomized

	Total cells		Ventral nucleus		Dorsal nucleus	
	R	L	R	L	R	L
$\bar{X}$	167 500	174 800	122 000	126 600	45 500	47 900
S	30 500	37 600	22 300	25 800	9 900	16 300
S	9 600	11 900	7 100	8 200	3 100	5 100
Controls						
$\bar{X}$	176 000		131 000		45 500	
S	15 300		9 400		7 200	
S_e	5 800		3 900		2 700	

$\bar{X}$ the arithmetic mean; S, standard deviation S_e, standard error of the mean.

Table II. *Statistics*

Cat no.	Total cells		Ventral nucleus		Dorsal nucleus	
	Right	Left	Right	Left	Right	Left
23	152 800	142 600	112 500	105 200	35 400	37 400
24	155 800	205 500	114 900	162 000	40 800	43 600
25	171 800	200 800	131 900	152 900	41 200	52 800
26	129 900	92 400	92 400	72 100	32 400	18 600
27	182 300	208 300	125 700	132 000	61 600	76 300
28	156 800	145 400	122 900	113 000	42 200	38 400
29	125 500	169 700	87 200	118 300	40 700	36 800
30	216 500	201 900	156 500	141 200	53 100	62 200
31	213 000	188 900	152 800	134 300	60 200	54 600
32	170 500	192 400	122 800	134 500	47 800	57 900

as well as on the noise-exposed side of the animals. It was seen convincingly in the cochlear nuclei and also but to a much lesser degree, in other cell groups seen in the same preparations, for instance the superior olives or the cerebellar nuclei. The various groups of cells in the cochlear nuclei, e.g. the great and the small spherical cells, the pyramidal cells of the dorsal nucleus or the octopus cells, were affected to a varying degree but it was not possible from the microscopical examination to evaluate whether there was any difference in the reactions on the labyrinthectomized and the noise-exposed side. They both seemed equally affected. It was expected that a counting of the number of cells on each side would reveal some differences, either when compared with each other or with the normal material. The results of the countings showed that no significant difference was found between the number of cells in the operated cases and the controls (Tables I, II, III).

Furthermore, there was no significant difference between the two sides (labyrinthectomized and noise-exposed) neither regarding the total number of cells, nor the two main nuclei seen apart. Thus it may be stated that neither labyrinthectomy nor exposure to noise has induced any numerically demonstrable loss of neurons in the cochlear nuclei.

Table III. *Controls*

	Total	Ventral nucleus	Dorsal nucleus
	195 600	141 700	54 000
	192 700	136 500	56 300
	164 900	121 300	43 700
R.	175 400	133 400	42 000
L.	151 200	115 200	36 100
R.	176 400	136 600	40 900
L.	177 500	132 000	45 500

DISCUSSION

On the left side the degeneration of the nerve cells might possibly be due to the fact that their afferent fibres were cut and the hair cells destroyed. However both the efferent fibres following the bundle of Oort and the intrinsic fibres inside the nuclei may supply enough stimuli to prevent degeneration. This may account for the preservation of the cell population of the labyrinthectomized side. However we are also presented with degeneration of nerve cells induced after noise. This is more difficult to explain. Artifacts may give similar pictures, but in these cases all precautions were followed during perfusion, and normal cats undergoing the same infusion procedure did not show similar pictures. It may be that the findings are significant, and if so these cells would be functionally impaired, and induce a recruitment phenomenon through a break in the central pathways of the inhibition reflex. This pathway occupies three neurons, the cells of the spiral ganglion, the Octopus cells of Osen (1969) and the cells of the retro-olivary nucleus, possibly omitting the

efferent bundle of Rasmussen. If this constant inhibition should fail because of lesions of the pathway strong signals would be perceived unimpeded, and a recruitment phenomenon might occur Further investigations e g. electronmicroscopy were suggested, whereby a more thorough examination of the nature of the cell changes might be possible

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EFFECTS OF NOISE UPON THE UPPER FREQUENCY LIMIT OF HEARING

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Abstract. The results of a thorough hearing examination in *228* young people *indicate that the upper frequency* limit is very sensitive to acoustic trauma, and that deviations from normal threshold are found more frequently above 5 000 Hz than at 3 000–4 000 Hz.

The Norwegian Broadcasting Corporation educates its own technicians and invites, each or every second year young people with examen artium perfect hearing and vision to apply for admission to the school. The selected students have a thorough audiological examination before they are finally accepted.

MATERIAL AND METHOD

Since 1954 I have performed this audiological examination, and since 1961 the testing and recording of data have been standardized. The material consists of 228 students from the classes 1962 to 1971 (201 males and 27 females) average age 20.7 years.

The testing was carried out in a soundproof and anechoic chamber starting with an otoscopic examination. Detailed pure tone audiograms covering the frequency range 125 Hz – 12 000 Hz were obtained by means of a Peters Audiometer (SPD 2 and AP 6) calibrated to ISO-threshold values.

Regular speech audiometry with monosyllabic numbers and PB-words was performed together with a randomized changing of intensity level between 40 dB and 100 dB Loudness balance test (Fowler) examination of possible diplacusis binauralis, determination of difference limen for frequency and for intensity and measurement of the upper frequency limit were performed. A Radiometer HO 12 Oscillator and Tandberg HI FI Loudspeaker system 15 were used in the free-field listening tests.

The upper frequency limit was determined for one ear at a time, the listening ear turned towards the sound source. The tone, at a constant sound pressure level of 80 dB was continuously varied so as to cross the upper frequency limit in both an ascending and descending fashion The SPL was determined using a Brüel & Kjær Precision Sound Level Meter at the place of the subject's ear after the subject had been removed.

RESULT

The observed sensorineural hearing losses were found in the frequency range above 2 000 Hz and were considered to be caused by exposure to high intensity sounds. According to the audiograms the material has been divided into 3 groups:

1 Deviations less than 10 dB between 125 Hz and 12 000 Hz: "Perfect Threshold" 113 subjects (50 %).

2. Deviations less than 30 dB (and greater

Table I. *Distribution of observed threshold deviations at various frequencies (in per cent)*

Above 5 000 Hz only	80 (63)
At 3 000–4 000 Hz only	10 (5)
Both at 3 000–4 000 Hz and above 5 000 Hz	10 (32)

The numbers in parentheses are results from a similar investigation in 1962.

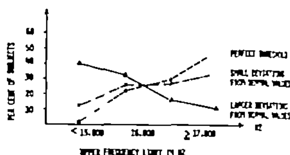


Fig 1 Observed upper frequency limit as percentage of subjects in each group

than 10 dB): "Small Deviations from Normal Threshold" 67 subjects (29%).

3 Deviations of 30 dB or more at one frequency or 25 dB at two adjacent frequencies: "Larger Deviations from Normal Threshold" 41 subjects (21%)

Of the 50 cases of noise-induced hearing loss (group 3) 34 were unilateral and 16 bilateral.

Examination of a possible difference between the male group having served in the military forces and the group without such service resulted in a higher percentage of noise induced hearing loss among male students being exposed to military noise—32% versus 18%

The most frequently observed "dips" are localized in the frequency range above 5 000 Hz (Table I) The observed upper frequency limits are presented in Fig. 1 Almost half of the group with "Perfect threshold" had an upper frequency limit above 17 000 Hz, whereas only 10% with Larger Deviations from Normal Threshold was able to hear frequencies above 17 000 Hz. Of this latter group 40% did not hear tones of frequency higher than 15 000 Hz, whereas only 1% of the group with Perfect Hearing had such a poor upper frequency limit.

The group with Small Deviations from Normal Threshold shows results lying between the other groups.

DISCUSSION

The findings in this selected material indicate that acoustic trauma causes threshold deviations most frequently occurring above 5 000 Hz, and brings about a reduction of the upper frequency limit, even in cases with small deviations from normal threshold. Three different reasons are suggested as possible explanations:

1 Most ear defenders, most ear mufflers and some ear plugs have less attenuation above 5 000 Hz than between 2 000–4 000 Hz (own measurements)

2 Resonance effect of the ear canal (Wiener 1947 Djupesland & Zwislocki, 1972), effects of sound diffraction around the head (Wiener & Ross, 1946) and effects of the auricle under different sound incident angles (Berland & Nielsen 1968) result in increased pressure at the ear drum in the entire frequency range above 2 000 Hz, compared with the sound field with subject removed. Various resonance tops are seen in this higher frequency range.

3 The organ of Corti probably has poorer blood supply towards the base at least in some individuals (Siebenmann, 1894) and stria vascularis here appears poorly developed (Axelsson, 1968)

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BRIEF TONE AUDIOMETRY IN PATIENTS WITH ACOUSTIC TRAUMA

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Abstract Temporal integration of acoustic energy has been investigated in 25 persons with an acoustic trauma. The investigation showed a descending ability to integrate acoustic energy with increasing hearing loss for the frequencies 2 000, 4 000 and 8 000 Hz. These results were compared with results from a group of presbyacusis patients, and it was shown that the relationship temporal integration/hearing loss is almost identical. A characteristic feature was normal temporal integration for some frequencies and abnormal temporal integration for others within the same ear Taking the histopathology on noise-damaged cochleae into consideration, esp. localized hair cell degeneration, it seems a necessary condition that the outer hair cells are intact, in order to achieve a normal temporal integration.

The perception of brief tones is dependent on the stimulus duration in the following way: when halving the stimulus time, the sound energy must be doubled to maintain the threshold or to achieve equal loudness. This phenomenon is called temporal integration (T I) and is investigated by brief tone audiometry

MATERIAL AND METHOD

Twenty-five patients are investigated. The diagnosis acoustic trauma" is supported by case history and a typical audiogram

The investigation is a monaural threshold determination performed in a sound-proof room. Each patient is tested at 3 or 4 of the frequencies 500, 1 000 2 000 4 000 and 8 000 Hz, and care has been taken to measure frequencies with normal as well as increased threshold in each ear For each frequency investigated, ten threshold measurements are made using impulses of varying length from 1 000 msec to 1 msec. Procedure of investigation rise–decay time, frequency characteristics of the impulses etc. are described earlier (Pedersen & Elberling, 1972)

The method of calculating the T I is illustrated in Fig. 1 The measured threshold relative to threshold for long tones are plotte in a double logarithmic coordinate system. regression line for the plotted values is cal lated and the area determinated by X-axis, the Y-axis and the regression line is used as the relevant expression for the T I (Pedersen & Elberling, 1972).

RESULT

A typical record from one patient is illustra in Fig 1 and serves to demonstrate normal as well as abnormal T I. within the same ear

In Fig 2 the T I. at 4 000 Hz is correlated to the actual hearing loss. The figure shows that the T I. decreases when the hearing loss increases. Same results were found at 2 000 and 8 000 Hz. In Fig. 2 the results at 4 000 H from patients with acoustic trauma are compared with the results from 46 presbyacusis patients.

DISCUSSION

It has been demonstrated that the T.I. is reduced in patients with acoustic trauma, and

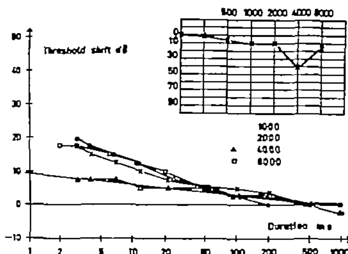


Fig. 1. Brief tone audiometry at the frequencies 1 000, 2 000, 4 000 and 8 000 Hz in a case of acoustic trauma. Audiogram upper right. The fig. shows normal temporal integration at the frequencies 1 000, 2 000 and 8 000 Hz, while the temporal integration is small at 4 000 Hz (14; normal value 28).

that the threshold shift obtained when using a long and a short tone impulse decreases, when hearing loss increases. The change in T.I. for a given hearing loss was almost the same as found in a group of presbyacusis patients (Pedersen & Elberling, 1973).

Degeneration of outer hair cells and nerve fibres in the cochlea is the characteristic finding in animal experiments on acoustic trauma. The localization and degree of degeneration being dependent on stimulation time, frequency and intensity (Engström et al., 1970).

In human cochlea too it has been possible to demonstrate a relation between acoustic trauma and localized hair cell degeneration (Bredberg, 1968).

The results of *brief tone audiometry* on persons with acoustic trauma (Fig. 1), showed normal and abnormal T.I. for different frequencies, within the same ear. Comparing these results with the localized hair cell degeneration in acoustic trauma patients, it seems reasonable to conclude that intact outer hair cells are necessary for normal T.I. of acoustic energy.

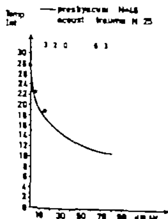


Fig. 2. Temporal integration correlated to the hearing loss at 4 000 Hz for patients with acoustic trauma. The values are pooled into 10 dB groups. Number of cases in each group are indicated. —— mean values of temporal integration in 46 patients with presbyacusis.

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BINAURAL DISCRIMINATION OF "EVERYDAY" SPEECH

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Abstract The binaural intelligibility of Pb-words in 9 indoor everyday listening situations is tested on 63 persons with bilateral sensori-neural losses and 22 normals. A group with bilateral sensori-neural loss of 50 dB or more on 3 000 Hz and above and normal hearing up to and including 2 000 Hz have 25–45% lesser scores than normals. The corresponding figures for bilateral normal hearing up to 3 000 Hz and bilateral sensori-neural loss of 50 dB or more on 4 000 Hz and above is 5–15%. In quiet there is about 5% difference between normals and these groups.

Kryter et al. (1962) and Harris (1965) have shown that the three most important frequencies in the tone-audiogram for estimating speech intelligibility of English Pb-words and sentences in "everyday situations" are 1 000 2 000 and 3 000 Hz. In order to investigate the importance of a hearing loss of frequencies over 2 000 Hz in such situations, nine different simulated listening situations in "everyday milieu" have been recorded The recording room was the sitting-room of a three-room flat. This had an area of 20 m² a volume of 50 m³ and a reverberation time of 0.5 seconds. The recordings have taken place over an artificial head without auditory canals. The speech signal, noise and competing speech have been presented via separate loudspeakers. In situations 7–9 (see below), the competing speakers have been authentic, and only the speech signal has been presented via loudspeaker The following listening situations have been recorded.

1 Signal noise = 0 dB 2 Signal noise = −5 dB 3 Signal noise = −10 dB 4 Signal/noise = 0 dB + competing radio voice 5 Signal noise = −5 dB + competing radio voice 6. Signal noise = −10 dB + competing radio voice	Distance, speaker to listener = 3 m.
7 Signal + 1 competing speaker 8 Signal + 2 competing speakers 9 Signal + 3 competing speakers	Distance between all speakers (incl. signal) and listener = 1 m.

Recordings 1–6 simulate a listening situation with and without competing radio voice and a traffic noise level of 63–73 dB (A) outside the window if the latter is of normal construction. In newly built houses there are windows where the outdoor level would correspond to 68–78 dB (A). The playbacks have taken place at the same level as the recordings and have been presented to 22 normal-hearing persons and 63 with sensori-neural loss, via binaural headphones. The hard-of-hearing persons have been divided into groups. The two most interesting of these consists of a group L 3 000 of 22 persons with normal hearing up to and including 2 000 Hz and thereafter binaural hearing loss of 50 dB or more at 3 000, 4 000, 6 000 and 8 000 Hz and a group L 4 000 of 6 persons with normal hearing up to and including

3 000 Hz and thereafter 50 dB hearing loss or more at frequencies 4 000, 6 000 and 8 000 Hz. In a comparison between these groups and the normal hearing persons, one finds that the binaural speech intelligibility in a quiet milieu, for normal hearing as well as for the two groups with hearing loss, is 90–95%

The listening situation signal/noise = 0 dB + competing radio voice simulates a fairly normal background noise + 1 competing voice in a room with closed windows in an urban residential area. One finds in this situation that group L 3 000 with hearing loss of frequency 3 000 and above has 30–40% speech intelligibility while the normal hearing persons have 70–75%

Group L 4 000 with normal hearing up to and including 3 000 Hz, has in this situation hardly 60%. If one converts the speech comprehension percentage for Pb-words into a corresponding one for sentences, one finds that the group L 3 000 misunderstands every third sentence in this listening situation while the normal hearing group only misunderstands every twentieth. In the situation with 1 speaker and 3 competing speakers, which simulates an everyday situation which is particularly common, one finds that group L 3 000 has 25–30% speech intelligibility of Pb-words while normal hearing have 65% Group L 4 000 has 50% Converted into sentences, this means that group L 3 000 misunderstands every second sentence, while a normal-hearing only misunderstands one of 20 A comparison between the performance of normal hearing and that of so-called slightly hard of hearing" persons in more or less difficult listening situations, which are daily typical for the greater part of the population, shows that one attaches far too little importance to hearing losses of frequencies over 2 000 This is due to the fact that speech intelligibility has hitherto chiefly been measured in quiet surroundings, which when it concerns diagnostic tests is naturally necessary When it is for the purpose of getting a grasp of the handicap of a hard-of-hearing person in everyday milieu" however judging by the result of this present work, it is hardly relevant. The author therefore suggests that the battery of tests which the otologist of today has at his disposal, should be further increased by one, namely speech intelligibility in "every day milieu"

A correlation analysis has been carried out, whereby those recordings which have given the greatest correlation to hearing loss, according to the tone-audiogram have been chosen Comparison has been made between listening with headphones and in sound field which has shown that headphone listening gives as good or somewhat better results than sound field listening. The hard-of hearing groups and the normal group with which they were compared, have gone through a lesser verbal test which shows that the vocabulary of the test persons, has not affected the test result.

Comparison between a group who have retained information on frequency 3 000 in only one ear while overlying frequencies have a hearing loss of 50 dB or more (L 3 000) and the groups L 3 000 and L 4 000 (50 dB or more bilaterally on frequencies 3 000 resp. 4 000 and above) has been carried out. This shows that speech intelligibility is fundamentally dependent on the better ear in a listening situation where there is a diffuse noise while an asymmetric hard-of-hearing person needs two good ears to a higher degree in a listening situation like that of signal + 3 competing speakers.

Eight groups of 7–10 normal-hearing medical students (a total of 64) have been tested in groups, each on a filtered version of three of the above mentioned recordings, i.e. signal/noise = 0 dB, signal/noise = 0 dB + radio and signal + 3 competing speakers. The result of this investigation shows that a falling off of frequencies over 2 500 Hz gives as great a loss of speech intelligibility as a falling off of frequencies below 1 000 Hz and that frequencies over 3 200 Hz are just as important as those below 700 Hz.

A comparison has been made between normal hearing who were tested on low-pass fil-

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tered speech (artificial hearing loss) and persons with corresponding sensori-neural loss. The result shows that the persons with hearing loss did not get better results than the corresponding artificially injured groups. To sum up the investigations show that one should allot great hearing losses on frequencies 3 000 and 4 000 Hz, just as much importance as great losses on frequencies 500 and 1 000 Hz, when estimating a person's speech intelligibility in "everyday milieu"

French & Steinberg (1949) developed a method whereby one could calculate from purely physical measurements, an index to the intelligibility of speech. They called this the Articulation Index or AI. AI calculations have been carried out for listening situation S/N = 0 dB, in unfiltered version, and in 7 filtered versions, and for listening situation S/N = −5 dB and S/N = −10 dB. Comparison has been made, between the expected result applicable to a vocabulary of 1 000 English Pb-words and the results received in the investigation. It shows that our results agree well with those expected, in spite of the material being Swedish Pb-words. This supports the view that a Swedish Articulation Index would not differ materially from an English one. Corresponding AI calculations have also been made for the hard-of-hearing groups and the results show that the expected speech intelligibility according to a vocabulary of 1 000 English Pb-words agrees closely with the actual result of our investigations. This means that AI calculations for persons with sensori-neural loss on frequencies over 2 000 Hz listening on speech in diffuse noise is a good method for estimating speech intelligibility

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COMMUNITY DIAGNOSIS OF PROFESSIONAL NOISE TRAUMA

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Abstract. 92 367 persons in all of Denmark applied for hearing rehabilitation in a 5-year-period, and of those 7 108 (7 7%) were registered under the diagnosis professional noise-induced hearing loss i.e. an incidence of about 1 400 per year or 28 per 100 000. 40% were below 65 years of age, and only 6% were women. There are estimated to be 6 000 industrial works employing about 50 000 persons at present with a continual noise level of more than 90 dB (A). A hearing conservation program has been proposed to The Ministry of Work.

Denmark has a population of 4 9 mill. inhabitants, who are carefully registered from birth until death. Since 1951 every Danish citizen with permanent hearing impairment may have complete rehabilitation free of charge including 1 or 2 modern hearing aids from the current market. Therefore very few people buy a hearing aid of their own, and thus the group of hearing handicapped persons passing through the hearing clinics indicates the morbidity nearly 100% The hearing aids are supposed to last for at least 5 years, concerning adults, and only in exceptional cases are the patients examined more than once in a period of 5 years.

METHOD

Information was collected from the three state hearing rehabilitation centres and their nine daughter clinics concerning the morbidity of clinical hearing impairment. To even out yearly variations, data were collected over a 5 year period during the years 1964–1970. The criteria for the diagnosis degeneratio nervi acustici professionalis are normal otoscopy nearly symmetrical hearing loss on both ears with a maximum around 4 000 or 6 000 Hz and a case history that the subjects have been exposed to relatively long periods of loud industrial noise, in which speech at a normal level could not be perceived at a short distance.

RESULT

In the 5 year period 92 367 patients who felt permanently hard of hearing applied for an audiological examination and rehabilition. Among those 7 108 = 7 7% are registered under the diagnosis: degeneratio nervi acustici professionalis. The important fact of this is that about 1 400 new patients per year are applying for audiological treatment, because they feel hard of hearing in their daily life due to noise exposure, i e. 28 per 100 00 inhabitants. More detailed information has been gained from three hearing clinics, to which 16 671 patients applied because of a permanent hearing disorder 1 108 patients are registered as chronic noise trauma (6.6%). Of those, only 6% were women, and 60% of the patients with noise induced hearing losses were over 65 years of age. In Table I the 1 108 patients are grouped according to their speech reception threshold. 200 had a normal speech reception threshold, although they had a noise dip. Half of the patients are registered with a slight impairment, 300 as medium, 80 as severe and finally 23 as deaf From the case records of the

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Table I *Severity of noise trauma indicated by Speech Reception Threshold*

Normal hearing	
SRT 0–20 dB	– 200 persons (18.0 %)
Slight impairment	
SRT 25–40 dB	– 505 persons (45.6 %)
Medium impairment	
SRT 45–60 dB	– 300 persons (27.1 %)
Severe impairment	
SRT 65–80 dB	– 80 persons (7.2 %)
Deaf	
SRT >85 dB	– 23 persons (2.1 %)
Total	– 1 108 persons

tients it is quite obvious that some patients get a severe noise trauma after a few years exposure, while other patients maintain nearly *normal hearing regardless of 20–30 years exposure* to heavy noise.

Noisy Industries in Denmark

Only about 25 factories have more than 1 000 workmen. The great majority of Danish industries have less than 25 employees. On one large island (Fyn) with around 700 000 inhabitants the representation of various kinds of industries is typical for Denmark. This area has been carefully explored, and from the results we estimate that we have, in Denmark as a whole 6 000 enterprises with a continuous noise level of 90 dB (A) or more In these enterprises about 50 000 workmen are employed. It is calculated that the noise level could be reduced to less than 90 dB (A) by means of moderate expenditure in approximately 80 % of these factories. In the remaining works in which noise cannot be reduced below the risk level the employees must make use of ear protectors, which are regarded as a last resource Engineers and medical audiologists have proposed to The Ministry of Work a detailed hearing conservation program with education of audio-technicians who should regularly perform audiometric examinations in industries. The effort should be concentrated around every new person who is going to be employed in industry with heavy noise. These new persons should have taken their pure tone audiogram in course of the first weeks of the employment. Then they should be followed with an interval of half a year with a control of the air conduction curve only in *respect of the frequencies 2 000, 4 000, 6 000* and 8 000 Hz. If the hearing deteriorates more than 10 dB the employee should consider being placed in a more quiet part of the enterprise.

DISCUSSION

The influence of noise upon human beings is *dependent on the noise level, the noise spectrum*, the duration and the individual's resistance to noise Like other sense organs, hearing is subject to a certain degeneration dependent of age. In a person with a noise-induced hearing loss this loss will be added to the hearing loss of aging. It is therefore usual that people with occupational hearing losses get along quite well through their thirties and forties, until they come to the age of 50 Then they begin to feel their hearing handicap more and more. This means that the noise wears out the reserves 10–20 years earlier than we would have expected due to the aging process. Most workmen ignore this happening. Therefore we have the task which is necessary to obtain the noise level which we want, and it is important that not only the physicians but all audiologists and the employed persons themselves are active in the abatement of harmful noise.

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A METHOD FOR COMPUTERIZED CLASSIFICATION OF PURE TONE SCREENING AUDIOMETRY RESULTS IN NOISE-EXPOSED GROUPS

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Abstract Screening audiometry data from noise-exposed groups are automatically processed by a computer. The process results in a two digit number for each individual showing the hearing situation for each ear The method has several advantages in that it is simple, rapid and inexpensive

Pure tone screening audiometry has become widely used as an important element of the hearing conservation programs for noise-exposed personnel. Usually only hearing losses exceeding a certain level (e.g. 15 dB) are recorded at selected frequencies (e g. 500 1 000 2 000 3 000 4 000, and 6 000 Hz).

This method is rapid and simple enough for non-specialized investigators to perform. Since there is a frequent occurrence of hearing defects in noise-exposed groups, civil and military health service programs reveal a variety of pathological conditions. Consequently there is an increasing demand for a rapid and uniform evaluation method to provide the basis for preventative measures.

The new method entails computerized classification based on reading of pencil marks from a new "Optical Mark Scoring Sheet" used during the screening process. This sheet has sections for marks of personal identification, hearing loss for each ear at the frequencies mentioned above, and for the otological case history with particular reference to noise exposure. The sheets are fed into an "Optical Mark Page Reader" connected to a computer (IBM 370/155 at the Uppsala University Data Centre). The marks denoting the hearing are converted by the computer into an individual two-digit number the first digit of which refers to the right ear and the second to the left.

The digits are from 1–5 depending on the extent to which the hearing losses involve certain areas of a pure tone audiogram sheet shown in Fig. 1 As an example, a two-digit number of 24 indicates "slight high tone loss" in the right ear and "severe high tone loss" in the left. A number of 35 indicates "moderate high tone loss" in the right ear and other hearing loss" in the left, the latter being of unknown type until further investigation has revealed its character

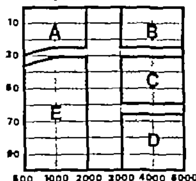
The two-digit number provides a fairly good view of the individual hearing situation especially in asymmetrical findings. First, a rough idea of the social hearing ability may be concluded from the lesser digit which refers to the better ear which is of dominant importance for the social hearing. Secondly the greater of the two digits, in case of asymmetrical hearing loss, indicates a hearing defect which is probably not caused by continuous acoustic trauma alone.

Previous methods have involved manual procedures and evaluations in which the da

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HEARING CLASSIFICATION

OF NOISE EXPOSED PERSONNEL



NORMAL HEARING RANGE (DIGIT 1) A B
SLIGHT HIGH TONE LOSS (DIGIT 2) A B C
MODERATE — — (DIGIT 3) A B C D
SEVERE — — (DIGIT 4) A B+C+D+E
OTHER HEARING LOSS (DIGIT 5) A B E / B C D E

▬ ALL MEASURED VALUES WITHIN THE AREA
– SOME MEASURED VALUES WITHIN THE AREA

Fig 1 The audiometric criteria according to which the marks denoting hearing loss are converted by the computer into a digit 1–5 for each ear

of both ears have been weighed together into one single expression (Heijbel & Lidén, 1957 Lindqvist, 1970) This may be insufficient in cases of asymmetrical defects of differing character The new method of classification has the additional advantage of being fully automated. The optical mark scoring sheets used at screening can be mailed directly to the data centre and the classification results are rapidly obtained The results may be stored for follow-up and for additional statistical processing of any desirable aspect. With the aid of a short instruction manual the need for otologic specialist consultation may generally be limited to some of the cases in which digit 4 or 5 occurs.

Finally the method is very inexpensive as compared to other approaches to the problem.

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A HEARING CONSERVATION PROGRAMME FOR SMALL INDUSTRIES IN A SWEDISH COUNTY

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Abstract Östergötland's County Council has organized an industrial hearing conservation programme mainly aiming at small industries where knowledge and own resources presumably are small. At a subsidized cost the programme offers noise measurements, screening audiometry information on noise control and ear protectors and a full audiological examination of certain cases. During 1971 we visited 65 companies. The results of screening audiometry (3 500 cases) and audiological examination of 212 cases are presented and discussed.

During recent years a growing need has been felt for studying industrial noise and preventing its damaging effects on exposed people. Although not sufficient, considerable activity has been going on for several years in Sweden, e.g. through health services organized by some, mainly larger companies, through the Labour Inspectorate, through some industry oriented projects, etc. In our early sporadic attempts in this area we found a great need for a permanent organization, preferably with a close medical connection. The problem is essentially one of information—informing the employer that improvement in noise levels in the long run is beneficial for production and means less risk of hearing loss and less discomfort for his employees, informing the employee that in too high noise levels not only his neighbour's but also his own hearing is at risk, that signal-to-noise ratio is sometimes better with ear protectors than without.

This permanent organization was established in 1971 as a part of the Department of Audiology at the Regional Hospital, Linköping. A special committee was organized, representing all the groups that have any interest in the programme (County Council, hospital, Labour Protectorate, labour unions, employers) to determine the general plans and rules of the programme. The staff consists of one electrical engineer one audiometrician and a secretary plus a consulting engineer equipped with a bus with a small sound-insulating box for audiometry audiometer sound level meter tape-recorder for recording transient sounds and an assortment of different types of ear protectors.

We have access to the company-register of the district office of the Labour Protectorate and contact mainly small firms (up to 100 employees) in risk-industries (metal, wood, printing, chemical, textile, food, stone). We offer our noise-programme at a subsidized cost (approx. one-quarter of the real cost) During 1971 we contacted ca. 200 small industries by mail, of which 23% wanted to be included in the programme. Another 12% could be persuaded adding up to 35% positive, 36% negative and 29% offering no response at all to our letter This must be interpreted as a rather moderate interest from the employers' side in our programme, probably partly due to ignorance of noise as a problem, partly due to economic considerations—not so much out of a fear of the cost of this programme, as of the demand for an improved working environment that might follow

Sixty-five companies were visited noise and hearing measurements performed and informa-

tion given on noise reduction and ear protectors.

After analysis of the noise measurements and application of risk criteria a written report is sent to the company Audiograms are classified in five categories according to a rather simple system suggested by Drettner et al. (1970). Before audiometry everybody is instructed to fill in a questionnaire, giving some personal and anamnestic data. The results of the audiometric classification together with these questionnaires are then studied in order to select those who ought to be subjected to a full audiological examination. A report on this classification and selection is sent to the company including a special letter of information to those who were found to have a slight, moderate or moderately severe hearing loss, presumably due to noise exposure. Based on the screening audiometry of the total material (3 543 cases) 32.5% were found to have bilateral hearing thresholds which were classified as normal (maximum 35 dB at 250 Hz, 30 dB at 500 Hz and 25 dB at 1 000–6 000 Hz) while ca. 8% were classified as bilateral severe hearing loss, presumably noise induced (severe loss defined by threshold exceeding above mentioned limit at some but not all frequencies in the range 250–2 000 Hz in ...n to the high frequency loss)

The group selected for further examination ...sists of three subgroups: (A) Cases with considerable asymmetry in the audiograms. (B) Cases with severe loss presumably due to noise, particularly those of young age (C) Cases whose audiograms indicate other types of hearing loss than noise-induced, previously undiagnosed

Out of the 3 543 audiograms obtained in 1971 212 cases (6) were selected for further examination. Category A made up 27 cases B 60 and C 125 cases In 8 of the cases in category A the most likely diagnosis remained noise-induced hearing loss after audiological examination while in category B this was true for 48 cases. The original preliminary diagnosis of noise-induced loss for the remaining 19+12 cases (35%) proved to be incorrect. In category C, 39% had a conductive hearing loss and 40% a sensori-neural loss most likely not caused by noise exposure. Six of the conductive cases have accepted offers of middle-ear-surgery Eight cases have obtained hearing aids and 14 cases other technical aids for the hard-of hearing.

In this selected group a comparison has been made between hearing thresholds obtained in the clinic and in our field-bus. The mean differences and standard deviations obtained were -2.1 ± 9.8 dB at 250 Hz, -0.9 ± 8.1 dB at 1 000 Hz and -0.9 ± 7.2 dB at 4 000 Hz with clinical thresholds in average better The standard deviations are somewhat larger than might be expected (Delany 1971) which may be explained by TTS at the field-audiometry by a disproportionately large number (10%) with temporary loss due to upper respiratory infections in the selected group, untrained and unsophisticated listeners, etc.

A check-up has been done on the accuracy of the manual use of the classification system for audiograms. Out of 500 randomly selected audiograms, 3% had been wrongly classified.

A system for the classification of audiograms is valuable since it offers a relatively clear view of the status of hearing in a population. If the number of classes is small and clearly defined audiometrically it will also be quite simple to use manually However if the classification is done automatically e.g. by a computer simplicity is no longer an important advantage, and the diagnostic accuracy should be improved by using a more sophisticated system

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PROPHYLACTIC MEASURES AGAINST INDUSTRIAL NOISE

A Fifteen year Survey of the Work done in a Swedish County

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Abstract. During a 15-year period there has been a successive and successful prophylactic work against industrial noise in the county of Örebro, Sweden. Medical as well as technical advice is given to the industries; informative courses are given, too.

The building up of small hearing centres in the various counties of Sweden started in the 1950s. One of the first of these centres was in the county of Örebro, the population of which is about 280 000

To start with basic audiometry was performed, but the major aim of the hearing centre was to channel the prescription and the selling of hearing aids in a firm and ethically correct way The senior physician of the ENT-department, two so-called "hearing assistants" and one audiometrist were responsible during the first years for the hearing rehabilitation program. Later a social worker was attached to the hearing centre.

As there was a great interest in the county council of Örebro in hearing rehabilitation and in hearing prophylaxis some screening investigations were also undertaken. The most natural one was—as in other hearing centres of Sweden—the screening made in ordinary schools, but in Örebro there also started a screening of the hearing of the workers at the Central Workshops of Swedish Railways. For various reasons, however the investigations were not carried out on a continual basis, though in 1957 a technician was employed at the hearing centre He was expected to do some repair work on hearing aids and diagnostic equipment, and to start a hearing investigation program for the noisy industries.

Only one factor in the county had at that time a good prophylactic hearing program—Bofors AB The other factories, small as well as larger ones, had only a summary survey of their noisy conditions, made by the Yrkesinspektion (the Swedish Factory Inspectorate).

The hearing centre offered its equipment and technical assistance to the firms, and medical advice was also included in this. After the investigations of the noisy parts of the factory were completed, attention was turned to the individual worker and his hearing. All those working in more than 85 dB (A) were to be examined at least once a year Information and advice was to be given. All the costs for the hearing centre were met by the firm itself

A very slow and modest start was a good help to consolidate the work, obtain experience and make improvements. A good deal of the early work was propagandistic, i.e., to inform the firms and the workers about the possibilities in this part of the health program.

After some years there was a stand-still until in 1966 an engineer with the sole task of dealing with the acoustic problems, especially industrial ones, joined the staff of the hearing centre. In fact, he turned out to be the first one in Sweden employed by a county council at a hearing centre to combat noise. Since

tion given on noise reduction and ear protectors.

After analysis of the noise measurements and application of risk criteria a written report is sent to the company. Audiograms are classified in five categories according to a rather simple system suggested by Drettner et al. (1970). Before audiometry everybody is *instructed to fill in a questionnaire, giving* some personal and anamnestic data. The results of the audiometric classification together with these questionnaires are then studied in order to select those who ought to be subjected to a full audiological examination. A report on this classification and selection is sent to the company including a special letter of information to those who were found to have a slight, moderate or moderately severe hearing loss, presumably due to noise exposure. Based on the screening audiometry of the total material (3 543 cases) 32.5% were found to have bilateral hearing thresholds which were classified as normal (maximum 35 dB at 250 Hz, 30 dB at 500 Hz and 25 dB at 1 000–6 000 Hz), while ca. 8% were classified as bilateral severe hearing loss, presumably noise induced (severe loss defined by threshold ex*ceeding above mentioned limit at some but not* all frequencies in the range 250–2 000 Hz in addition to the high frequency loss).

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MUSIC—A NOISE HAZARD?

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Abstract. Measurements of music noise spectra in various youth centres show great variations in levels in rooms with different acoustic properties. The noise spectra from different orchestras are, however remarkably equal. The high level and the narrow dynamic range, together with the likelihood of being very close to the loudspeakers give reason to believe that the criterion of damage risk is surpassed by listeners and musicians rather frequently Actual hearing measurements seem to confirm this suspicion.

During the last 10 years not only has unwanted environmental sound increased in intensity but also recreational sound, such as the music played by pop groups" and performed in discotheques.

Although most measurements of such musical sounds seem to indicate intensity levels above or on the borderline of damage risk criteria, the observations of music-traumatic" hearing losses vary from place to place. Ewertsen (1971) concludes that in Copenhagen no cases of deafness caused by pop music" have been seen among 80 000 individuals with hearing loss examined.

Lipscomb (1970) found a significant increase in hearing loss in the frequency range above 3 000 Hz among college students and concluded the findings to be tangible evidence of the toll being exacted by pop music" sounds.

Speaks et al. (1970) having measured music noise spectra and temporary threshold shifts summarize their results: the exposures are borderline"

My investigation of the hearing status of broadcasting technicians starting their training (Flottorp 1972) indicates that incidence of acoustic-traumatic hearing loss among young people has increased during the last 10 years. In order to examine whether a possible causality exists between this observation and the exposure young people get to music noise in youth centres, I have measured the sound level in several such centres in the Oslo area.

APPARATUS AND METHOD

The measurements were carried out with a Precision Sound Level Meter (Brüel & Kjær type 2201) calibrated with a Pistonphone (Brüel & Kjær type 1613) Sound levels were measured at several locations on the general dancing area and at restaurant tables, as close to the loudspeakers as listeners used to come and at more distant places.

Usually a frequency analysis in octave bands was done, though a number of measurements were made using the A-weighting network.

The slow" response was mainly used, however some measurements of drum-noises were taken using the fast" response. An estimated average of frequent peaks observed on the meter was recorded.

RESULT

The results for some orchestras are presented in Figs. 1–2. There is remarkably good agree

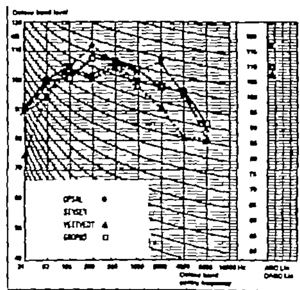


Fig 1 Music noise" in various youth centres in Oslo.

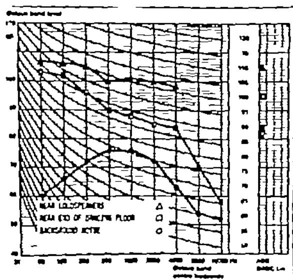


Fig 2 Music noise" at various distances from the orchestra "Beatnics"

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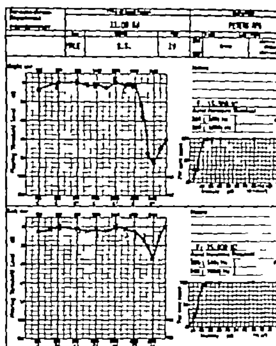


Fig 3 Hearing loss in a rock-and-roll musician.

The sound pressure level in octaves abov 4 000 Hz depend very much upon the distanc from the loudspeakers, because the crowd c young people absorbs much of the energy i the highest frequency range

In the rear part of the dancing floor th sound spectrum is completely different fro that in the front part, as shown in Fig. 2.

The reverberation time of the actual hal also is an important factor in the resultin spectrum and sound pressure level at th listener s place Very often, basements ar used for youth clubs, and here the reverbera tion time may amount to 3–4 seconds. It i not unusual that such basements are used i schools for training and rehearsals by th school s brass band The sound level in suc rooms is definitely higher than when the sam band performs in an acoustically treated room or a larger room.

Quite a few youth clubs and discotheque have rather short reverberation times, and th sound level of the music performed there ha been measured to be definitely lower than th results presented in this paper

DISCUSSION

A typical feature of modern "pop music" is its very narrow dynamic range. When the group starts, it immediately exceeds the normal maximum level of a symphony orchestra, and keeps this level within ±10 dB. This makes "pop music" much more hazardous to the hearing than music performed by great symphony orchestras.

Hi-fi amplification systems, with amplifiers yielding several hundred Watts, are used by the groups. Very often the loudspeakers are placed only 1 metre from the listeners, resulting in a sound pressure level at the listener's ear of 120–130 dB.

The loudspeakers are placed in front of the performing musicians. Very often, however, the hall and especially the stage accommodating the musicians is rather reverberant, causing very high levels at the ears of the musicians also. Many of the listeners are exposed to this type of music noise 2–3 hours almost each day and the musicians more than 6–8 hours a day.

Taking into account the possibility of getting very close to the loudspeakers and also the fact that rooms used for this type of music very often are too reverberant, I believe the borderline of damage risk criterion is probably surpassed by listeners and musicians rather frequently. The reported increase in noise induced threshold deviations (Flottorp, 1972) seems to confirm such a suspicion. An audiogram of a member in a "pop group"—not otherwise noise exposed—is shown in Fig. 3 as an indication of the hearing hazard of "pop music".

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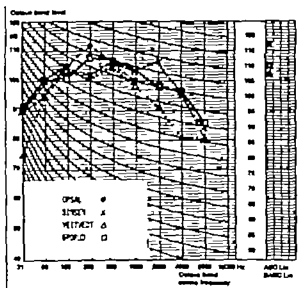


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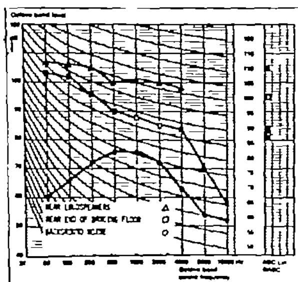


Fig 2 "Music noise" at various distances from the orchestra "Beatnics

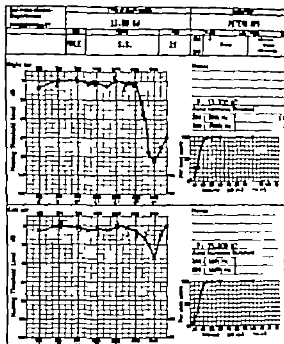


Fig 3 Hearing loss in a rock-and-roll musician.

The sound pressure level in octaves above 4 000 Hz depend very much upon the distance from the loudspeakers, because the crowd of young people absorbs much of the energy in the highest frequency range

In the rear part of the dancing floor the sound spectrum is completely different from that in the front part, as shown in Fig. 2.

The reverberation time of the actual hall also is an important factor in the resulting spectrum and sound pressure level at the listener's place Very often, basements are used for youth clubs, and here the reverberation time may amount to 3–4 seconds. It is not unusual that such basements are used in schools for training and rehearsals by the school's brass band. The sound level in such rooms is definitely higher than when the same band performs in an acoustically treated room, or a larger room.

Quite a few youth clubs and discotheques have rather short reverberation times, and the sound level of the music performed there has been measured to be definitely lower than the results presented in this paper

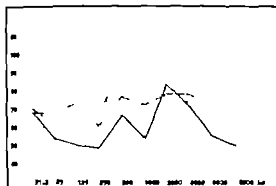


Fig 1 Signal of four different emergency vehicles. Measured with octave filter set.

ears, hearing at 60 dB level, or when using cotton prosthesis, at 30 dB was used as a handicapped subject Generally the hearing-handicapped subject heard the warning signals of emergency vehicle 10–30 m before or as quickly as the normal persons. The worse the attenuative properties of car bodies were, the better the hearing-handicapped subject was able to observe the warning signals.

Is there discrimination against hearing-handicapped persons in traffic? Would it not be better to take as criterion ear diseases rather



Fig 2. Traffic noise in street corner Total noise 76–92 dB (A). Measured with octave filter set. Average O maximal level.

Table I. *Attenuative properties of bodies of four cars in dB (A)*

	Sound source		
	Front	45° angle	90° angle
Bedford (truck)	21 dB (A)	25 dB (A)	19 dB (A)
Renault R 4	28	29	25
Saab 99	33	38	34
Toyota Crown	52	55	47

Table II *Subjective loudness of alarm signal in traffic conditions*

	Distance of emergency vehicle from street corner			
Warning signal heard	25 m	50 m	75 m	Total
At a distance before street corner	3	6	2	11
Immediately before street corner	14	7	10	31
In junction box	18	12	15	45
After street corner	1	3	9	13
Not heard	1	3	3	7
Total	37	31	39	107

41 drivers could not localize the emergency vehicle.

than hearing ability in the issuing of driving licences? One can ask too, is there discrimination against all drivers other than those of emergency vehicles? According to traffic law an emergency vehicle possesses the right of way Is a driver unprotected in court in a case involving collision with an emergency vehicle?

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SOUND PRESSURE DISTRIBUTION IN THE OUTER EAR

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Abstract Sound pressure transformation between several points in the outer ear and the eardrum was measured by means of a probe-tube microphone. The tip of the probe tube was positioned with the help of a fine screw arrangement and a Zeiss surgical microscope. The results slightly amend and extend the classical data of Wiener and Ross

It is known that the sound pressure at the entrance of the ear canal is not the same as the sound pressure at the eardrum except at very low audible frequencies. The variation of sound pressure along the human auditory canal was measured in a classical study by Wiener & Ross (1946) with the help of a small probe-tube microphone The sound pressure distribution in the ear canal has been computed theoretically by means of an electrical network model (Zwislocki 1965). Small discrepancies have been found between the analog results and the experimental results of Wiener and Ross. In order to find the reason for the differences and ascertain as accurately as possible the sound pressure distribution in the ear canal, we repeated and extended Wiener and Ross's measurements with somewhat modified equipment. While so doing, we paid particular attention to a careful determination of the points of measurement

MATERIAL AND METHOD

Seven healthy randomly selected subjects (3 female and 4 male age 16–44 years) with clinically normal outer ear and normal hearing were used. The subject was positioned on an examination table in a soundproofed chamber with acoustically treated walls and ceiling. The subject's head was placed sideways on a cork filled cushion (the left ear always towards the cushion) and fixed to the examination table by means of an adjustable belt The right ear faced the sound source an Altec 405E loudspeaker mounted on a square baffle (2 feet on each side) hanging from the ceiling, 110 cm above the entrance of the ear canal. A Brüel & Kjær Beat Frequency Oscillator Type 1022, served as the signal source. The frequency was swept from 20–20 000 Hz. The signals were amplified and delivered to the loudspeaker

The sound pressure was measured by means of a Brüel & Kjær 1/2-inch condenser microphone connected to a 50 mm long tube of 1 mm outer diameter Since we were only interested in sound pressure ratios at each frequency no probe tube corrections had to be introduced. Using a finely threaded screw at the microphone holder and a Zeiss surgical microscope the probe tube was advanced into the ear canal, and the sound pressure was measured at. (1) 1 mm above the tympanic membrane at the umbo (2) 1 cm below the entrance (3) the entrance of the ear canal, (4) the tip of the tragus, and (5) 1 cm above the tragus. The sound pressure was recorded on a Brüel & Kjær level recorded (2305A). The sound pressure at the above-mentioned locations in the outer ear and the length of the ear canal were measured 6 times on each subject.

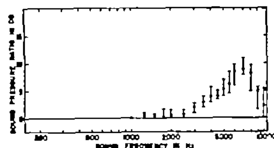


Fig 1 Sound-pressure transformation between the eardrum and a point in the ear canal at 1 cm from the entrance. Circles indicate the medians; vertical range bars, the interquartile ranges.

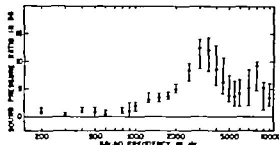


Fig 3 Sound-pressure transformation between the ear drum and the tip of the tragus. Circles indicate the medians, range bars, the interquartile ranges.

RESULT

The mean length of the ear canals was 23 8 mm in the male and 22 mm in the female group. The overall mean of our population amounted to 23 mm. The results of the sound pressure measurements are shown in Figs. 1–4 They are expressed as ratios between the values obtained at the eardrum position and at the other positions.

Median sound pressure levels which are plotted in Fig. 2 by means of filled circles, do not generally follow the typical values. Because individual resonance frequencies vary along the frequency scale, the resulting median resonance frequencies vary along the frequency scale, the resulting median resonance peak should be somewhat broader than a typical peak. This is so mainly because peaks found in individual ears are not at exactly the same frequency In order to investigate the size of the effect, all the individual data were normalized with respect to a median frequency of the peak, which was found to lie at 3.5 kHz. The solid curve in Fig. 2 approximates the normalized medians. It seems to be shifted somewhat towards lower frequencies relative to the non-normalized medians. However the width of the peak is practically unchanged. The correction introduced by the normalization may be regarded as negligible.

The sound pressure ratios between the ear drum and a position located 1 cm outside the tragus are plotted in Fig. 4 The first peak occurs at 3 kHz and the second, at 6 kHz. Both peaks are almost fused, so that a substantial enhancement of sound pressure takes place in the broad frequency range between 2 and 8 kHz. According to model experiments

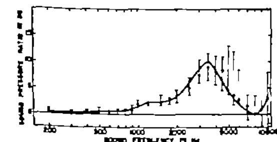


Fig 2. Sound-pressure transformation between the ear drum and the entrance of the ear canal. Circles indicate the medians; vertical range bars, the interquartile ranges. The solid curve averages the data after normalization with respect to the frequency of the main maximum.

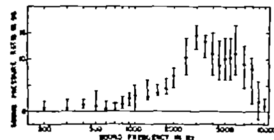


Fig 4 Sound-pressure transformation between the ear drum and a point at 1 cm outside the tragus. Circles indicate the medians; range bars, the interquartile ranges.

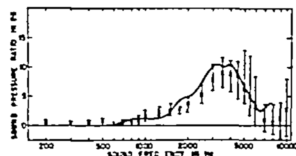


Fig 5 Sound-pressure transformation between the ear drum and the entrance of the ear canal. Crosses indicate the means, range bars, the interquartile ranges. The solid line reproduces corresponding data of Wiener & Ross (1946).

by Shaw & Teranishi (1968), this effect is due to the quarter wave resonance of the concha.

DISCUSSION

Our data for the pressure transformation between the eardrum and the entrance of the ear canal deviate somewhat from those obtained by Wiener and Ross under similar conditions of the incident sound. The difference is illustrated in Fig. 5 where the solid curve shows Wiener & Ross's mean data, and the crosses, the means of our results. The main peak obtained by them is somewhat broader than in our investigation and is shifted somewhat towards lower frequencies. A secondary peak appears at 7.5 kHz. This pattern resembles the pattern found by us at the tip of the tragus (Fig 3). We suspect that Wiener & Ross had the tip of their probe tube located between the entrance of the ear canal and the tragus rather than directly at the entrance. Our results are in close agreement with computations obtained with the help of an electrical network analog (Zwislocki, 1965) and with data obtained by Teranishi & Shaw (1968) on a geometric model of the outer ear The only appreciable difference occurs at the maximum and is most probably due to a difference between the acoustic impedance at the eardrum and the acoustic impedances terminating the model-ear canals.

Our data should be useful for practical purposes, such as the design of couplers for earphone calibration, evaluation of ear protectors, and transfer of sound-pressure specifications from one point in the outer ear to another From a fundamental point of view they demonstrate the contribution of the outer ear to the amazing sensitivity of the auditory system to sound. As is shown in Fig. 4 the outer ear enhances the sound pressure at the eardrum by between 1 and 9 kHz, a frequency range of 8 kHz. The maximum at 3 kHz amounts to about 15 dB.

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COURSE OF AND SEQUELAE TO 248 PETROSAL FRACTURES

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Abstract The course of and sequelae to 26 transverse and 222 longitudinal fractures of the petrous portion are reported. Most patients were followed for a long time and seen 2–7 years after the trauma. Hearing loss of the conductive type has a very favourable prognosis, but for therapeutic and insurance reasons the patients should be followed.

A material of severe cranio-cerebral and other multiple traumas is difficult to follow and treat. This perhaps is the explanation why the literature contains only a few major series of petrosal fractures followed over a long period or after-examined. Owing to the good communication and collaboration between the specialities, we have been able to follow 248 petrosal fractures until the condition became normalized or stationary The majority of patients were seen at follow-up 2–7 years after the injury

The material comprises 230 patients admitted with *fresh* fractures from 1962–1968 In 18 the fracture was bilateral. The most common causes were automobile accidents and run-over accidents (42%) falling off bicycles, mopeds, or scooters (25%), fall or crash (28%) Children and adolescents predominated, only 41 patients being over 50 whereas 51 were 0–10 years. The petrosal fracture often co-existed with other cranio-cerebral injuries, such as cerebral contusion (25%) thecal fracture (27%), and concussion (35%).

Transverse fractures

Twenty-six patients (10%) had transverse fractures with destruction nystagmus, extinguished vestibular function and anacusis. The two last-mentioned signs were also present at follow-up. Radiologically the fracture was demonstrable in 69% of the cases.

Longitudinal fractures

Longitudinal fractures were present in 222 cases and were demonstrated radiologically in 50% According to the findings in the auditory canal and in the middle ear the longitudinal fractures were divided into cases with rupture of the drum (128), meatal fractures without rupture of the drum (38), and haematotympanum (51). In 41% of the cases of this latter group the fracture in the petrosal part could be demonstrated radiologically In several cases it could be seen subcutaneously in the meatus *or as a fracture of the theca coursing towards* the petrous portion.

One week after the trauma the perforation had closed in all patients but 27 3 weeks after in all but 7 Three months after the trauma the perforation had closed in all the patients, so that early myringoplasty is hardly indicated. Haematotympanum subsided in 3 weeks in practically all cases. The delayed closure of the perforation was due in 7 cases to major dry perforation, in 7 to persisting otorrhoea of cerebrospinal fluid which also subsided spontaneously in all cases, and in 13 to acute infection although 9 of them had received prophylactic penicillin. Prophylactic penicillin *therapy probably does not reduce the incidence* of infection and is in my opinion unnecessary

Table I *Hearing in the 500–2 000 cps range primarily 3–6 weeks after and 3 months to 7 years after the injury*

dB-Interval	Primarily	3–6 weeks after	3 mo.–7 years after
0–20	54	139	176
21–30	55	34	9
31–40	32	8	10
41 50	34	11	6
51–60	17	6	5
Over 60	11	5	6
Not examined	19	19	10
Total	222	222	222

113 patients were treated prophylactically with penicillin and 80 were not. 8% and 5% respectively developed acute infection which however did not cause major therapeutic problems.

Vestibular signs, such as spontaneous nystagmus, positional nystagmus, and reduced vestibular function were found initially in 22% also equally distributed on the various groups of fractures.

The primary hearing loss may often (in 24%) be within the normal range (0–20 dB Table I). 3–6 weeks after it had returned to normal in 63%. The greater the primary conductive hearing loss the less the chance of rapid normalization and the greater the likelihood of dislocation or fracture of the ossicular chain Some eous improvement occurred in nearly all cases during the first 3 weeks, except in patients with perceptive hearing loss. If hearing of the conductive type was still poorer than 30 dB 6 weeks after the trauma, the cause was always ossicular dislocation or fracture However spontaneous improvement may occur 6 weeks after the trauma, but it is slight and rare The final hearing status 3 months to 7 years after the trauma was as follows: 80% had hearing with the normal range in the frequency group 500–2 000 cps, but in 20% the hearing of the conductive type was 5–10 dB poorer than in the non-damaged ear In 21% there was slight perceptive hearing loss of 10–25 dB for the range 4 000–8 000 cps, and in 6% there was moderately severe hearing loss of 20–60 dB for the range 2 000–8 000 cps, but most marked for 4 000 cps. In 13% (28 cases) there was ossicular dislocation or fracture Of these patients 10 had moderately severe to severe perceptive hearing loss of high tones and partially also of low tones. A total of 8 patients (3.5%) had perceptive hearing loss of low tones, not improved since the trauma.

Out of 28 patients with ossicular dislocation or fracture 16 underwent operation. 10 were not diagnosed until at follow-up, indicating that in spite of all the testing after the trauma failed in some cases. There were several types of dislocation, most often of the long process of the incus towards the handle of the malleus (5 cases) superiorly associated with fracture of the stapes (3 cases) or posteriorly (3 cases). As a rule interposition of the incus was performed. The results were good (Tos, 1971), giving an average hearing gain of 30 dB, average postoperative hearing 21 dB 12 patients were not operated upon Hearing improved spontaneously in 6 there occurring spontaneous fibrous connection between the stapes and incus or spontaneous myringostapediopexy

Peripheral facial palsy was observed in 44 patients. In 10 it occurred immediately after the trauma. In these cases the prognosis was poor there being one year after the trauma —in spite of operation—still one total and 6 partial palsies. In 34 cases the palsy was tardive occurring 1–7 days after the trauma. In all these patients it had completely disappeared as early as 3 months after the trauma.

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FRACTURE OF TEMPORAL BONE, EARLY OR RETROSPECTIVE DIAGNOSIS, AND SURGICAL HEARING RECONSTRUCTION

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Abstract Among the victims of acute skull trauma, temporal bone fracture is found in 6–8% An early diagnosis emerges from clinical inspection, X-ray ex posure and is strongly supported by otoscopy The otologist is concerned about the facial nerve immediately after the fracture and to detect signs of defects which call for decompression. The destiny of hearing is due either to cochlear damage or alterations in the ossicular mechanism. Conductive hearing loss possibly resulting from previous skull trauma may benefit from surgical intervention in the tympanic cavity

All patients in Oslo who fall victim to head injury are admitted to the Department of Neurosurgery in the Municipal Hospital. During the years 1964–68 temporal bone fracture occurred in 8.4% of head traumas. During 1970–71 the rate was 6% and 120 patients were investigated as a material of interest within the field of traumatic otology

Table I. *Diagnostic results from X-ray examination (120 cases)*

Survey of skull on admission		
Fracture of temporal bone demonstrated		90 (75%)
Fracture of temporal bone not demonstrated	30	
Special exposure of primary neg. cases		
Fracture of temporal bone demonstrated		14
Fracture of temporal bone not demonstrated	16	
		104 (86.7%)

The diagnosis temporal bone fracture was identified clinically as meatal bleeding in 76% X-ray survey of the skull gave the diagnosis in 75% Supplementary otoscopy demonstrated hemotympanum in those not having visible external bleeding. Guided by otoscopy which revealed hemotympanum special X-ray ex posures of the temporal bone itself increased the total score of X-ray positive findings to 86% In the remaining 14% the diagnosis had to be based upon the clinical examination (Table I)

Along with the fracture diagnosis the facial nerve function must be checked. Any paresis or paralysis registered within 12 hours after injury indicates a probable lesion of the nerve trunk, usually between the knee and the styloid

Table II *Temporal bone fracture involving the facial nerve (120 cases)*

Onset of palsy related to injury	Peripheral	Central
Within 12 hours	[illegible]	[illegible]
Between 12–48 hours	3	
After 2 days	4	
After 5 days	5	
	14 (11 7%)	
Restored facial function in	12	

1 nerve decompression performed. The patient died 2 months after injury 1 patient died 4 days after injury

1 patient died 3 days after injury 1 patient alive with permanent paresis.

Table III *Hearing situation among surviving patients*

Included in scheme	120	
Deceased within 1 14 days	23	
Survivors		97
Subject to perceptive loss		
slight to severe	7 (7.2)	
destroyed cochlea	7 (7.2 ,,)	14 (14.4)
Subject to conductive loss		
transitory and restored to normal		78 (80.4)
qualified for hearing reconstruction		1 (1 •)
Not available for follow-up		4

foramen. Early appearance of nerve damage calls for decompression with opening of the facial canal. When paresis occurs after a latency of 24–48 hours the prognosis is good, even without operation (Table II).

During convalescence following the fracture one has to identify the nature of an initial hearing loss, whether conductive or perceptive A fracture may cause damage to the ossicles. In some cases a subsequent exploration of the tympanic cavity discloses a disorder of the ossicular chain which can be restored (Table III).

This experience should encourage the otologist to look for a possible connection between a conductive hearing loss and previous head injuries. The interval between a head trauma with persistent conductive loss and the retrospective diagnosis of temporal bone fracture varies from months to years. Special X ray exposures and tomography of the temporal bone itself are a valuable aid to preoperative assessment (Table IV).

The case history roentgenography and audiological measurements can justify exploratory measures. A great variety of ossicular defects are encountered and can be dealt with (Table V).

In large cities the majority of fractures are caused by traffic accidents. A large number arise from sports and industrial activity A number of elderly people get injured in their homes (Table VI).

Table IV *Repair of fracture interval and X-ray diction*

Case no	Age	Interval between injury and op. (years)	Preoperative roentgenography	Observation period (years)
1	1	4/1	Fracture of pyramid	‿/12
2	11	4 1	Fracture of squama	4/12
3	32	5/1	Fracture of squama	5
4	23	7/1	Fracture of squama	2
5	61	1	Fracture of squama	1
6	37	15	Negative	1
7	30	16	Negative	10,1
8	22	16	Fracture of squama	-
9	65	53	Fracture of squama	14/1

Table V *Repair of fracture findings and method*

Case no.	Age	Operational findings	Method	Thresholds and gain (dB)
1	12	Chain intact	Explor only	65-65 – 0
2	11	Crural fracture	Piston on plate	58-33 – 13
3	3	Luxation of stapes	Reduct.	50-10 – 40
4	‿3	Adhesions	Debrid.	38-28 – 10
5	61	Incus and stapes destroyed	Explor only	58-50 – 5
6	37	Luxation of stapes	Reduct.	43-25 – 18
7	30	Long proc. defective	Incudo-staped. tubing	47 33 – 14
8	22	Long proc. missing	Interpos. of incus	47-8 – 39
9	65	Bridge fracture, mall. joint defect.	Cloth pin synthesis	7? 55 17

Table VI *Circumstances leading to temporal bone fracture (120 cases)*

Traffic accident	47 (39.2 %)
Violence or assault	14 (11.6)
Injuries other than above	59 (49.2)

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ISOLATED FRACTURES OF THE STAPEDIAL ARCH

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Abstract The most frequent traumatic lesion in the middle ear is the luxation of the incus, which is seen in the three-quarters of all cases. The isolated fracture of the stapedial crura accounts for the majority of the remaining cases and contains interesting aetiological, diagnostic and technical operative problems.

MATERIAL

Out of 50 traumatic lesions of the ossicular chain we have seen 11 cases of that kind at the ENT-department in Aarhus. Seven out of these 11 patients are from 5 to 15 years old. Two resulting from transmeatal traumas, the rest from severe cranial traumas where 8 of these had been unconscious with bleeding from the ear 8 of the patients were handicapped by a tinnitus which disappeared post operatively

Examinations and diagnosis

An X ray examination including tomography of the temporal bone has proved worthless in this connection but was at least able to ex clude a luxation of the incus. Only in 2 cases was a longitudinal fracture of the temporal bone demonstrated. Preserved reflex of the stapedius muscle was found in 4 cases and in 2 of these the reflex of the tensor muscle elicited *a.m* Klockhoff was increased. As a sign of an increased looseness in the ossicular chain/ear drum system, we accepted this and therefore confirmed the suspicion of an isolated fracture of the stapes.

Operative findings

All cases showed a fracture of the stapedial arch close to the footplate as the only defect. In 1 case, however a small remnant of the stapes footplate was left on the anterior crus. In 3 cases the stapedial arch was displaced to the promontorium.

RESULT

Fig. 1 shows the average hearing improvement of each patient, illustrated by a column. Patients 1-4 had the sound transmission system re-established by means of the incus as a columella between the stapedial footplate and the ear drum. Nos. 5-7 had the function of the ossicular chain re-established by interposition of a polyethylene tube or like no. 8 an autogenous bone graft between the footplate and the incus. In nos. 9-11 a simple reposition of the fracture was performed with interposition of a small bone fragment in the fracture line, as in case no. 9

In all cases the stapedial footplate was preserved. The postoperative hearing threshold is in all patients 30 dB or better and the average hearing gain for the whole series is about 27 dB

DISCUSSION

The way in which the craniotraumatic stapes fracture arises is very complicated, and it might be seen together with a luxation or subluxation of the incus at least. The direction and course of the fracture lines in the skull together with the displacing forces at the moment of the trauma, the strength of the fixating ligaments, the joint capsules and ossicles must be pieces in that puzzle which

Table III *Hearing situation among surviving patients*

Included in scheme	120	
Deceased within 1 14 days	-3	
Survivors		97
Subject to perceptive loss		
slight to severe	7 (7.2)	
destroyed cochlea	7 (7_)	14 (14 4)
Subject to conductive loss		
transitory and restored to normal		78 (80.4)
qualified for hearing reconstruction		1 (1)
Not available for follow-up		4

foramen. Early appearance of nerve damage calls for decompression with opening of the facial canal. When paresis occurs after a latency of 24–48 hours the prognosis is good, even without operation (Table II)

During convalescence following the fracture one has to identify the nature of an initial hearing loss, whether conductive or perceptive A fracture may cause damage to the ossicles. In some cases a subsequent exploration of the tympanic cavity discloses a disorder of the ossicular chain which can be restored (Table III).

This experience should encourage the oto-

Table IV *Repair of fracture interval and X-ray rediction*

Case no.	Age	Interval between injury and op. (years)	Preoperative roentgenography	Observation period (years)
1	1	4 1	Fracture of pyramid	_/1_
_	11	4 1	Fracture of squama	4/1
3	3	5 1	Fracture of squama	5
4	23	7/1_	Fracture of squama	2
5	61	1	Fracture of squama	1
6	37	15	Negative	1
7	30	16	Negative	10,1
8	22	16	Fracture of squama	2
9	65	53	Fracture of squama	14/1

Table V *Repair of fracture findings and method*

Case no	Age	Operational findings	Method	Thresholds and gain (dB)	
1	1_	Chain intact	Explor only	65–65	0
2	11	Crural fracture	Piston on plate	58–33	+18
3	32	Luxation of stapes	Reduct.	50-10	40
4	23	Adhesions	Debrid.	38–28	10
5	61	Incus and stapes destroyed	Explor only	58–50	5
6	37	Luxation of stapes	Reduct.	43–25	18
7	30	Long proc. defective	Incudo-staped. tubing	47 33	14
8	22	Long proc. missing	Interpos. of incus	47–8 –	39
9	65	Bridge fracture, mall. joint defect.	Cloth pin synthesis	7' 55	+17

Table VI *Circumstances leading to temporal bone fracture (120 cases)*

Traffic accident	47 (39.2 %)
Violence or assault	14 (11 6)
Injuries other than above	59 (49.2)

logist to look for a possible connection between a conductive hearing loss and previous head injuries. The interval between a head trauma with persistent conductive loss and the retrospective diagnosis of temporal bone fracture varies from months to years. Special X ray exposures and tomography of the temporal bone itself are a valuable aid to preoperative assessment (Table IV).

The case history roentgenography and audiological measurements can justify exploratory measures. A great variety of ossicular defects are encountered and can be dealt with (Table V).

In large cities the majority of fractures are caused by traffic accidents. A large number arise from sports and industrial activity A number of elderly people get injured in their homes (Table VI).

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ONE THOUSAND MAXILLO-FACIAL AND RELATED FRACTURES AT THE ENT-CLINIC IN GOTHENBURG

A Two-year Prospective Study

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Abstract. A prospective study of 1 000 maxillo-facial and related fractures in 899 patients treated at the ENT-clinic in a city of 450 000 inhabitants during two years is reported with special reference to the frequency of different types of fractures and the etiology Fractures caused by traffic accidents tended to be more serious but injuries from assaults were quantitatively predominant. Alcohol consumption was often involved in cases of fractures from assaults and falls. The "hidden costs of alcohol abuse in the somatic care is pointed out.

In the town of Gothenburg with approximately 450 000 inhabitants there is only one ENT clinic. The maxillo-facial and related fractures seen at this clinic during the period July 1969 to June 1971 totalled 998 well-defined fractures which affected 899 patients. Often the care of the patients required the services of an odontologist and neurosurgeon, ophthalmologist and plastic surgeon, as additional consultants.

471 patients were treated as outpatients and 428 were hospitalized. 670 operations were performed on 622 patients 277 patients were treated conservatively *The age distribution* showed a majority of injured in the age group of 20–29 years. *The sex distribution* in the total material was 5 men to 1 woman In the temporal fracture group the conditions were, men to women 10 1

This study was supported by grants from AB Fylgia

Fracture distribution (Table I)

The number of nasal fractures was high, as expected (39%) The zygomatic-maxillary fracture group (22%) includes the important group of fractures which involve the orbits. The number of fractures of the mandible was high (20%) and this seems to imply the use of brute force in the material and makes the analysis of the causes specially interesting. The number of temporal fractures (7.5%) agrees well with the other material. The number of *frontal sinus fractures* seems low but the latter depends upon the fact that a relatively large number (17 cases) are again found in the combined fracture group. In the group of combined fractures are included 38 cases of the mid-face fractures (Le Fort I, II III).

Table I *Fracture distribution*

	Number of		
	Patients		
	n		*Fractures*
Nasal fractures	350	39	
Zygomatic-maxillar	196	22	
Mandibular	185	20	803
Temporal	68	7.5	
Frontal sinus	4	0.5	
Combined	96	11	195
Total	899		998

Table II. *Causes of fractures*

Fracture type	Cause				
	Traffic	Assault	Falls	Sport	Other
Nasal	37	160	66	60	27
Zygomatic maxillar	30	93	38	[illegible]	[illegible]
Mandibular	33	98	35	6	13
Temporal	24	13	[illegible]	3	3
Frontal sinus	–	1	0	1	0
Combined	46	33	14	1	–
Total	172 (19)	398 (44)	178 ([illegible])	94 ([illegible])	57 (6)
No. of patients 899					

Causes of fractures (Table II)

Assaults are a strongly dominant cause (44%) and the most common fracture is a nasal one. The high frequency of mandible fractures agrees well with the brute force trauma which is often given by kicking a person who has been knocked down.

Traffic injuries. Fractures caused by traffic accidents accounted for 19% in the total material and were qualitatively more severe owing to the high frequency of combined fractures. Among the traffic injuries the number of patients with temporal fractures was highest (36 cases) when isolated fractures of the temporal bone and those in the combined fracture group are added together. Often the temporal fractures occurred in combination with skull base fractures and concussion.

Among traffic injuries 81 protected (car borne) road users were affected compared with 87 unprotected road users (not in cars). Drivers without safety belts were injured in 46 cases, while in 4 cases injury occurred to drivers with safety belts, but the latter were in any case only slight. None of the front seat passengers (19 cases) who were injured had worn safety belts. Even if the material in the viewpoint of safety belts and their importance is strictly limited, it is in agreement with the great traffic injury material which shows the value of safety belts *partly* by lowering the number of traffic injuries and *partly* by reducing the severity of the injury (Bäckström, 1963). The same experience applies to the unprotected road user material (motorcyclists) of whom 12 did not use the crash helmet, while 7 did wear one. The helmet seems to have protected them against the severe injuries.

Alcohol and fractures

An attempt to judge the importance of alcohol in connection with injury has been carried out. "Under the influence of alcohol on the occasion of the injury" was the judgement on those who showed clear signs of intoxication, smelled of alcohol and/or admitted taking alcohol. The connection between drinking alcohol and fighting seems obvious. In the group of mandible fractures 61% of the patients were under the influence of alcohol, when the cause has been fighting. The proportion of inebriates was even higher in the case of assaults in the temporal (85%), the zygomatic maxillar (66%) and the combined fracture groups (66%). 80% of the patients with temporal fractures after falls were intoxicated.

The distribution of the days of the week showed that the frequency of fractures, as well as the frequency of fractures in connection with alcohol consumption, showed a concentration around the weekend and this was especially applicable to the relation between alcohol and assault.

The investigation of the connection between alcohol and the occurrence of fractures, is an example of the "hidden" costs of alcohol abuse within the somatic care and the retarding effect on the care of sick persons with other somatic diseases in a position, where the supply of medical care does not meet with the demand.

From the continuing follow-up of the patient material only a few viewpoints are mentioned: *Nasal fractures* in the majority of cases have been treated traditionally with reposition under local anaesthesia and plaster and the patients treated as outpatients. Correcthe secondary

operations have only been necessary in a few cases.

Zygomatic-maxillary fractures have been treated according to Gillies (53%), or Gillies together with inter-osseous wiring (11%). Operation according to Caldwell-Luc with inter-osseous wiring was undertaken in 6% and Caldwell-Luc with antral packing in 11%. The relatively high frequency of operations according to Gillies with or without osteosuture speaks well for our good experience of this method.

Our attitude to *frontal sinus fractures* is active and 9 of 17 cases were operated upon with exploration in certain cases in combination with inter-osseous wiring or other form of fixation. Tomography agreed well with the findings at operation concerning the back wall of the frontal sinus. Neither in operated nor in non-operated cases have sequelae with liquor fistula or meningitis arisen.

The treatment of the *mandible fractures* may be seen in our second paper in this journal.

In conclusion we would like to stress the importance of training in this field of traumatology of the otolaryngologist and the odontologist. One of the arguments favoring this view is that these specialists are represented at the county hospital, where the fracture cases are mainly treated.

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COMPLICATIONS AFTER JAW FRACTURES

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Abstract 260 consecutive cases of jaw fractures were seen during a two-year period. A follow-up 6 months after treatment covering 81 patients showed that the dental injuries are the most important sequelae of a jaw fracture. The complications noted at treatment had been fewer except for the disorders of the temporo-mandibular joint which had an increasing tendency. It was striking to note the great falling off percentage of suspected alcohol abuses, i.e. patients injured by assaults and falls.

Jaw fractures in "the Gothenburg fracture material July 1969 to June 1971" presented in our preceding paper together with jaw fractures from Gothenburg Children's Hospital and Mölndal County Hospital from the same period were treated in cooperation between otolaryngologists and odontologists. Patients with fractures of odontological interest were ways seen during the acute phase by a dentist the Odontological Clinic, Gothenburg.

This report deals with the results obtained and special reference is given to the type and frequency of complications registered at the end of treatment and at follow-up 6 months later. The material comprised 260 patients. 212 cases (82%) were mandible fractures, 22 cases (8%) were mid-face fractures and 26 cases (10%) were combined mandible and mid-face fractures. With regard to the causes of the fractures the reader is referred to our preceding paper in this journal.

The treatment of the mandible fractures has fundamentally consisted of closed reduction and inter maxillary fixation. Inter-osseous wiring has been used in some cases mainly to get control over edentulous jaw fragments. Usually this management has been combined with inter maxillary fixation. Instead of wiring plates has been used in a few cases.

Mid-face fractures have in general been treated with internal osseous fixation to the malar bone or to the lateral orbit-edge in addition to inter maxillary fixation. The period of immobilisation has been 2–9 weeks with an average of 4 weeks. The short fixation times have as a rule applied to condylar and mid face fractures. Isolated condylar fracture was in most cases treated conservatively. Condylar fracture combined with other mandibular fracture were treated by fixation, the time being decided by the type of combined fracture symptoms and disturbances in the bite. Immediately after the immobilisation period jaw exercises were started.

Table I shows the type and frequency of complications at the end of the treatment. Teeth injuries were found in 67 cases (26%). A reduced ability to open the mouth—at opening the distance between the incisal edges of the frontal teeth was less than 40 millimetres—was noted in 49 cases (19%). Anaesthesia due to injury of the infraorbital or the inferior alveolar nerves was registered in 37 cases (14%). Disorders in the temporo-mandibular joint was observed in 9 cases (3%). Facial or jaw deformities or malocclusion were noted in a few cases.

So far 81 out of 260 patients have appeared

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Table I *Complications at the conclusion of treatment*

Type of fracture	No. of patients	Deformities of the face	Sensory disturb.	Temp.-mand. joint disorders	Restriction of opening	Mal-occlusion	Injuries of the teeth
Condyl.	60	1	1	4	9	1	8
Other mand.	101	3	16	4	11	1	24
Cond. + other mand.	51	—	6	—	20	2	17
Midface	22	—	6	—	1	1	13
Mandible + midface	26	3	8	1	8	1	5
Total	260	7	37	9	49	6	67

for the check-up 6 months after treatment. Presumably those with complications are over represented in this group, but a striking feature is the large percentage of falling off among the patients with a history of alcohol abuse and/or patients injured by assaults and falls. Thirty-one of the 49 patients with restriction of opening were seen at follow-up and only 9 (11%) showed persisting restriction. Anaesthesia was found in 11% but the observation period was too short to evaluate whether the nerve injury was permanent or not. It may be noted that the anaesthesia in the mentalis region did not show any quick regression. The frequency of disorders in the temporo-mandibular joint showed a tendency to increase already after this relatively short observation period.

In patients with complications after 6 months the follow-up period must of course be extended. Further cases of complications are also to be expected after this observation period, especially joint disorders. The dental injuries are of course permanent and often cause great psychological and also economical strain on the patients. In our experience quick reposition and fixation and administration of antibiotics, increase the chances for healing of injured teeth and alveolar processes. It is important not to neglect these injuries during the acute stage of the treatment of jaw fractures.

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CASES OF RECURRENT NERVE PARALYSIS IN GOTHENBURG FROM 1968–71

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Abstract. A study undertaken at the beginning of this century of the etiology of recurrent nerve paralysis was compared with a material from the present time. The comparison points to a changed pattern in the incidence of primary diseases.

Of all the works dealing with the etiology of recurrent nerve paralysis I have chosen to deal with the study by Paul Frenckner (1935) of 159 cases diagnosed at the ENT Clinic of Sabbatsberg Hospital, Stockholm, from 1903–1924 He also studied mortality for at least 10 years before publishing his results. The primary diseases behind the recurrent nerve paralysis in Frenckner's material are shown in Table I As in most other investigations, the "unknown etiology" group was the largest. If cases diagnosed as "rheumatoid arthritis" are included, the group with an obscure etiology comprised 1 4 of the total number of cases. Goitre heads the list of primary diseases, including both benign and malignant thyroid enlargement. Mortality amounted no less than 60% during the period of observation more than half of the deaths occurring the first year after the discovery of the recurrent nerve paralysis.

The present study is based on 57 cases diagnosed as recurrent nerve paralysis at their first visit to the phoniatric department of the ENT Clinic, Sahlgrenska Hospital, Gothenburg, Sweden, from 1968–71 Most of the patients were referred to the phoniatric department from the ENT and other hospital clinics. In some of the cases, the purpose of the referral was evaluation of the indication for voice therapy In other cases a subsequent follow-up by the phoniatrist was desired, even in the absence of voice disturbance. Postoperative cases following thyroid surgery were excluded from this material. The brief period of observation did not permit the tabulation of any relevant figures on mortality A summary breakdown of the material into main diagnostic headings is presented in Table II Paralysis unrelated to surgery occurred more than twice as often as in surgical cases. If the thyroidectomy cases had been included the relationship would have been the opposite Thoracic surgery is now the predominant cause of paralysis in surgical cases, while neoplasms are responsible for the majority of the pareses due to non-surgical causes. As Table III shows, 5 of the cases of unknown etiology displayed other cranial nerve symptoms at the time of the onset of the recurrent nerve paralysis, symptoms such as external eye muscle paresis, facial nerve paresis and pharyngeal paresis. These symptoms were mostly reversible and of shorter duration than the recurrent nerve paralysis. "Virus disease" was used as the presumptive diagnosis in cases with an infectious course, since no serological or virus isolation tests were made Table IV shows that mediastinoscopy caused the largest number of cases of recurrent nerve damage among the different surgical procedures presented in the present material. Remarkably enough, this is also the only diagnostic one

Table I. *Primary diseases in Frenckner's material from 1903–24*

	%
Unknown etiology	19.1
Goitre	12.1
Pulm. tuberculosis	10.6
Aortic aneurysm	9.9
Oesophageal cancer	8.5
Syphilis	7.8
Rheum. arthritis	5.7
Organic heart failure	5.0
Tumour (pulm., pleural & mediastinal)	4.3
Mammary cancer metastasis	2.8

In conclusion if we look back on Frenckner's study from the first few decades of this century we should be aware that he excluded all postoperative cases which he regarded as being without prognostic relevance. Thus, his results can only be compared with the group of non-surgical cases in my material. Etiological sources such as goitre, pulmonary tuberculosis, syphilis, unoperated aortic aneurysm an organic heart failure have become rare probably because of improved diagnostic and therapeutic methods. If the development of thoracic surgery vascular surgery and neurosurgery permits successful treatment of many conditions which previously brought about recurrent nerve paralysis and death, it seems likely that the surgeon in our time plays a greater causative role in recurrent nerve paralysis. Publications in recent years (Hahn, 1970) even claim that the cuffed tube used during general anesthesia may produce recurrent nerve paralysis as result

Table II. *Main diagnostic headings of the present material from 1968–71*

Diagnosis	No. of cases
Non-surgical (40 cases)	
Of unknown etiology	19
Tumour	10
Viral infection	6
Neurological disease	4
Trauma	1
Surgical (17 cases)	
Thoracic surgery (incl. mediastinoscopy)	11
Vascular surgery	3
Vagal neurinoma surgery	3

Table III *Etiology of the non-surgical cases*

Unknown etiology (19 cases)	
With other cranial nerve symptoms	5
Without other symptoms	14
Tumours (10 cases)	
Thyroid cancer	5
Lung cancer	2
Laryngeal cancer	1
Mammary cancer metastasis	1
Mb Recklinghausen	1
Viral infection (6 cases)	
With influenza-like symptoms	6
Neurological disease (3 cases)	
Cerebral palsy	1
Polyneuritis (Guillain–Barré)	1
Wallenberg syndrome	1
Trauma (1 case)	
Penetrating neck injury	1

Table IV *Etiology of the surgical cases. Thyroid surgery cases excluded*

Thoracic surgery (11 cases)	
Mediastinoscopy	6
Aortic aneurysm	2
Botallo's duct	1
Lung cancer	1
Benign pulmonary tumour	1
Vascular surgery (3 cases)	
Stenosis of com. carotid art.	1
Thrombosis of subclav. vein	1
Stenosis of subclav. art.	1
Vagal neurinoma surgery (3 cases)	
Vagal neurinoma	3

of local pressure damage. Parallels can easily be drawn with other medical fields in which prolonged patient survival has been accompanied by a higher incidence of various complications.

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ELECTROMYOGRAPHY IN MOTOR DISORDERS OF THE LARYNX

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Abstract EMG recordings have been performed from the cricothyroid and the vocal muscle in a series of patients with motor disorders of the larynx. Data obtained from 3 cases are reported. In one patient with idiopathic vocal cord paresis neurogenic lesions were found both in the vocal and in the cricothyroid muscle In another patient subjected to thyroid surgery and in a third patient suffering from dysphonia bilateral lesions were demonstrated in the nerves to the cricothyroid muscles in both cases although there were no signs of abnormal mobility of the vocal cords at laryngoscopic examination. The results show that the EMG examination can disclose lesions in the motor nerves to the larynx which are not possible to reveal at clinical examination.

In a previous paper an electromyographic recording procedure was described which permitted identification of some 20 motor unit potentials from each normal vocal muscle (Knutsson et al. 1969) In that investigation 469 motor unit potentials from 18 normal muscles were identified, and the data collected could be used as a basis for prognostic evaluation in patients with a traumatic injury to the recurrent laryngeal nerve (Haglund et al., 1970) and also for an analysis of idiopathic vocal cord paresis (Haglund et al., 1972)

The results obtained in a recent investigation on the normal electromyogram in the human cricothyroid muscle (Haglund, 1973) provide further opportunities to reveal the existence of lesions of the motor nerves to the larynx which cannot be disclosed by e.g. indirect laryngoscopy stroboscopy and X ray examination. The present paper will describe the results obtained by electromyographic examinations of the cricothyroid muscle and the vocal muscle in some patients with motor disturbances of the larynx.

Case Reports

Case 1 was a 39-year-old man suffering for 7 weeks from a hoarseness with sudden onset. Indirect laryngoscopy showed that the left vocal cord was immobile in a paramedian position, but extensive clinical investigations failed to reveal any underlying cause and the paresis was thus classified as an idiopathic vocal cord paresis. In Fig. 1 the hatched columns of the histograms show the distribution of duration and amplitude of 13 motor unit potentials from the left cricothyroid muscle for comparison are included corresponding data from 338 motor unit potentials identified from 17 muscles in 13 normal subjects. In this case several of the potentials were of normal amplitude and duration, showing that a considerable proportion of the motor axons in the external branch of the superior laryngeal nerve were conducting nerve impulses. However in addition there was an increased incidence of potentials of a duration less than ms and, though not shown in the histogram, these potentials were of an amplitude below 150 µV thus indicating that they were fibrillation potentials. Thus many of the muscle fibres were denervated. Electromyographic recording from the left vocal muscle on the same occasion disclosed electrical silence indicating a total paresis of this muscle (cf Haglund et al., 1971).

Case was a 34-year-old man who had been subjected to bilateral resection of the thyroid gland because of atoxic adenomas. Since that time his voice was easily fatigued and he was unable to speak or sing at a high pitch. Indirect laryngoscopy immediately after the operation, as well as at the time of EMG recording 36 months later showed that the vocal cords had normal motility though the position of the right vocal cord was slightly lower than the left As appears from the histogram in Fig the left cricothyroid muscle had an increased incidence of potentials of a duration less than ms. These poten-

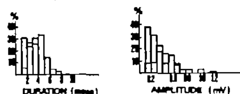


Fig 1 Duration and amplitude distribution of motor unit potentials recorded from cricothyroid muscle in Case 1 (▨) as compared with corresponding data from the normal material (□).

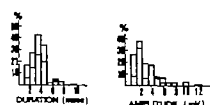
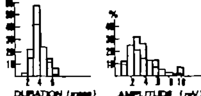


Fig 2 Duration and amplitude distribution of motor unit potentials recorded from cricothyroid muscle in Case 2 (▨) as compared with corresponding data from the normal material (□).

tials were of low amplitude, indicating denervation. In addition, out of the 35 potentials recorded 24% were polyphasic as compared with only 0–4% in the normal muscle (Haglund, 1972). These potentials were of high mean duration, indicating that re-innervation had taken place in part of the previously denervated muscle fibres. EMG recording from the right cricothyroid muscle showed signs of increased insertion activity and only four potentials were found, two of which had the characteristics of fibrillation potentials, thus indicating that a lesion was present also in the right external branch of the superior laryngeal nerve. Thus, while laryngoscopic examination in this case failed to give any conclusive information, EMG recording was a valuable adjunct in analysing the etiology of the voice disturbance.

Case 3 was a 17-year-old girl suffering from voice disturbances since childhood. The most prominent abnormality was a monotonous voice and inability to raise the pitch of the voice. The vocal cords had normal motility and position, and the patient was treated under the diagnosis of dysphonia. Fig. 3 shows the duration and amplitude distribution of the action potentials recorded from the right vocal and cricothyroid muscles. The potentials recorded from the right vocal muscle are of normal duration and amplitude and the interference pattern is complete. In the right cricothyroid muscle, however the mean duration of the potentials is increased and there is an increased incidence of potentials of long duration (range 6–9 ms) and such of high amplitude (range 900–2 800 microvolt). In addition, the majority of these potentials were polyphasic, thus indicating that re-innervation had taken place. The muscles on the left side showed a similar pattern, i.e. a normal pattern in the vocal muscle but in the cricothyroid muscle there were electromyographical signs of a lesion in part of the motor axons to the muscle.



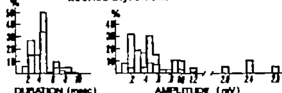


Fig 3 Duration and amplitude distribution of motor unit potentials recorded from vocal muscle (above) and cricothyroid muscle (below) in Case 3 (▨) as compared with corresponding data from the normal material (□).

The data presented show that EMG recordings from the laryngeal muscles may be of great value in voice disturbances of unknown origin.

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ENDEMIC RECURRENT LARYNGEAL NERVE PARESIS

Correlation between EMG and Stroboscopic Findings

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Abstract. Sixteen cases of recurrent laryngeal nerve paresis are presented, 8 bilateral and 8 unilateral. 13 of the 24 paretic vocal cords also had paresis of n. laryng. sup. Some patients had paresis of the face, tongue, velum or diaphragm. Only 5 vocal cords in 5 patients regained normal mobility during the observation period, one year and a half. EMG was correlated with stroboscopic findings and with the position of the vocal cords. Considerable reinnervation and normal vibratory mobility was found in 1 vocal cords within 10 months, but of these only abducted and adducted normally after more than 1 year. Our conclusions were: 1) Glottic wave depends on active tonus, i.e. innervation of the muscle in the actual vocal cord but does not necessarily imply functioning innervation. 2) The position of the paretic vocal cord depends, at least in part, on the degree of paresis.

During the winter 1969–70 an increase in the incidence of recurrent laryngeal nerve paresis appeared in several parts of Europe (Bauer 1971, Hefter & Bikistein 1970, Wirth & Leypoldt 1970). The patients were said to have been ill a few weeks previously with the so-called HongKong flu. After dubious cases had been sorted out 9 men and 7 women were left in our material, none of them younger than 30 years, with altogether 8 bilaterally and 8 unilaterally immobilized vocal cords. In spite of thorough investigations it has not been possible to ascertain the genesis, but the viral infection has been supposed to be the origin although the connection is somewhat uncertain.

Fifteen of the patients also had symptoms indicating affection of other nerves. Most of them had difficulty in swallowing, some of them so severe that they rapidly lost weight. Occasional paresis of the facial, vagus, hypoglossus and phrenic nerves were also found. In addition, several of the recurrent laryngeal nerve paresis cases seemed to be complicated by paresis also of the superior laryngeal nerves.

The diagnosis superior laryngeal nerve paresis, however, could not be made clinically in some of the cases, at least not from the supposition that if such a paresis was combined with a homo-lateral recurrent laryngeal nerve paresis the vocal cord should be in the intermediate position. In reality it was in such a case the quality of the voice and not the local findings, which aroused the suspicion, later to be verified by the use of EMG.

Larynx was inspected at rather short intervals using stroboscopic light. In 12 patients, 4 with bilateral and 8 with unilateral paresis of the recurrent laryngeal nerves, EMG was made from the vocal muscles and the cricothyroid muscles on both sides. Concentric EMG needles were used and put in place percutaneously. EMG was made on two occasions, about 5 months and about 10 months after the occurrence of the paresis.

To judge from the first EMG investigation 13 of the cricothyroid muscles were more or less paretic, 2 bilateral and 11 unilateral. Cor-

siderable reinnervation could be registered at the second EMG in all investigated cricothyroid muscles.

Out of the 24 paretic vocal cords normal or almost normal mobility could be found in only 5 after the complete observation period, a year and a half but none of these until after the first half year. This is considerably later than is usually the case in paresis of the recurrent laryngeal nerve.

At the second EMG investigation a good reinnervation could be registered in 12 of the still paretic vocal cords and at the same time good or even excellent glottic wave could be seen in stroboscopic light. Of these 12, however only 2 abducted and adducted normally after further more than 2 months, i.e. more than 1 year after the patients fell ill. In not a single one of the remaining immobilized vocal cords in this group with good reinnervation and good glottic wave was normal mobility found during the rest of the observation time.

As far as other symptoms are concerned it should be mentioned that all patients except one swallowed normally after usually less than half a year that a paresis of the facial nerve disappeared after less than a month, while a deviation of the velum in 1 patient and the deviation of the tongue in another patient remained unchanged during the whole period.

If EMG findings and stroboscopic findings are correlated it can be noticed that the presence of reinnervation in the vocal muscle corresponds very nicely to the occurrence of glottic wave in the vocal cord. As such a glottic wave can always best be seen at so-called chest register when the vocal muscle is active but not at so-called falsetto when the muscle is inactive it seems reasonable to suppose that the glottic wave depends on active tonus, in other words on the innervation of the muscle in the actual vocal cord (Fex, 1970). It should be stressed that such an innervation of one single muscle does not necessarily imply functional innervation in all the laryngeal muscles, which of course is necessary if one expects coordinated vocal cord function. In order to know the innervation of the different laryngeal muscles it is necessary to examine every single muscle with EMG. To form a general opinion and especially one about the state of innervation in the vocal muscle at phonation, however it is recommended to use the stroboscopic examination which is easy to perform and easy to undergo in other words, it is clinically practical.

The investigation also shows that just as partial paresis can be found in other parts of the body it can be found in the laryngeal muscles. This would appear to be completely obvious but has generally been surprisingly disregarded. In reality one has to take into account the occurrence of partial paresis as well as nonfunctional reinnervation. This is no doubt of importance for the position of the immobilized vocal cord. Likewise a moderate increase of innervation in a paretic cricothyroid muscle may suffice to explain a change in position from intermediate to paramediate in a paretic vocal cord.

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VOCAL CORD PALSIES FOLLOWING SURGERY FOR BENIGN NON TOXIC GOITRE

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Abstract The frequency of palsies of the recurrent nerve in a series of 271 patients undergoing surgery for nontoxic benign goitre is analysed in respect to the number of operated sides.

Meurman (1951) and Evoy (1961) have stated that the incidence of vocal cord palsies after thyroid surgery varies between 0 3% and 13 2% with primary operations and that it is much higher in reoperated cases. The reason for the variability is that the series are mixed regarding preoperative assessment, pathology and method of operation.

METHOD AND MATERIAL

Since 1963 at the E.N T clinic in Örebro we have used uniform methods for preoperative assessment, operative technique and postoperative follow up All patients subjected to thyroid surgery from 1964 to 1970 are included in this series except for cases of thyroid cancer or toxic goitre. The vocal cord function of all the patients was checked twice preoperatively Four types of operation were used.

1 *Enucleation of adenoma*

In these cases, n. recurrens was not identified and the thyroid arteries were not divided This method has only been used in case of superficial adenomata and when the risk of injuring n. recurrens has been judged as non existent.

2. *Resection*

The n. recurrens was identifie[illegible] the anterior th[illegible] art. was divided [illegible] jority of th[illegible] Only when a su[illegible] tion w[illegible] was this r[illegible]

3 *Subtotal lobectomy*

The n. recurrens was identified, both the superior and inferior thyroid arteries divided and a thyroid remnant was left.

4 *Total lobectomy*

The n recurrens was identified and the arteries were divided as in group 3 The surgery was performed leaving no macroscopic evidence of thyroid tissue.

Postoperatively the patients have been followed up for 1 to 8 years. Indirect laryngoscopy was performed at least 3 times in the first year and yearly thereafter The series consists of 283 patients (235 women and 48 men) of which 264 had adenomatous nontoxic goitre or solitary adenomata and 19 had thyreoiditis or adenomatous non toxic goitre with a proven histology of thyreoiditis. The second group were usually subjected to surgery because of suspected malignancy

Nine patients with preoperative palsies have been excluded from this series. One case had a large goitre and had emergency surgery because of respiratory obstruction. On preoperative examination the vocal cords were found in almost paramedian position but adduction was present. At operation the right n. recurrens was bluish and swollen which can be taken as a sign of degeneration. Postoperatively there was a right irreversible n. recurrens palsy Three patients with preoperative palsy eventually showed normal vocal cord function postoperatively That vocal cord palsy can be seen in non-malignant goitre is re-

Table I *Number of operated sides and palsies (261 patients having primary thyroid surgery)*

Type of operation	No. of sides	Total no. palsies Right/Left	Irreversible palsies Right/Left
Enucleation of isthmus adenoma	8	0/0	0/0
Enucleation of adenoma 20/18	38	0/0	0/0
Resection 32/36	68	1/0 (1.5)	0,0
Subtotal lobectomy 61/83	144	6/6 (8.3 %)	2/0 (1 4 %)
Total lobectomy 48/44	92	2/2 (4 4)	1/0 (1 1 %)

ported by Hall Allen (1967) and others. Thirteen patients who had been subjected to previous thyroid surgery are accounted for separately

RESULT

In order to judge the risk of dissecting the n. recurrens the number of sides operated have been used in this account. Therefore one patient can be accounted for twice if he had bilateral surgery Eight cases with only isthmus adenoma are not referred to as any side.

The table shows the number and distribution of operated sides and how the palsies are distributed between the different types of operation. After 46 enucleations and 68 resected sides there were no irreversible nerve palsies. Subtotal lobectomy was performed on 144 sides and there were 12 (8.3%) palsies of which 2 (1 4%) were irreversible, and total lobectomy was performed on 92 sides and there were 4 (4 4%) palsies of which 1 (1 1%) was irreversible.

No case of bilateral palsy was seen. The 3 irreversible palsies were all on the right and none were found in the thyreoiditis group.

Thirteen cases having previous thyroid surgery developed 3 irreversible palsies in 17 operated sides.

DISCUSSION

The total number of palsies following primary thyroid surgery in 261 patients was 17 (6.5%) of which 3 (1 1%) were irreversible. After 46 enucleations and 68 resections there were no irreversible palsies. In order to see the result of exposing the recurrent nerve one can compare the 144 subtotal lobectomies and the 92 total lobectomies with the corresponding groups of non-toxic goitre in Gisselsson's (1950) report. In his series there were 52 total lobectomies and 104 subtotal thyroidectomies, making a total of 260 ($52 + (2 \times 104)$) sides with 14 (5 4%) palsies of which 6 (2.3%) were irreversible In Gisselsson's cases the recurrent nerve was not exposed.

In the Örebro material there were 236 sides (144 + 92) in the subtotal and total lobectomy groups resulting in 19 (8%) palsies of which 3 (1.3%) were irreversible. In comparing these series it is found that a higher total number of nerve injuries results when the nerve is exposed but few irreversible palsies. Lahey & Hoover (1938) reported that in 3 000 cases they reduced the number of postoperative palsies to 0.3% by exposing the nerve In the reoperated group there were 3 irreversible palsies in 13 patients (17 sides) which illustrates the far greater risk of nerve injury in these cases.

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EXAMINATION OF VOICE FUNCTION OF PATIENTS WITH PARALYSIS OF THE RECURRENT NERVE

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Abstract 96 patients were examined when the diagnosis of paralysis was made, with indirect laryngoscopy determination of pitch and voice range, phonation time, respiration, stroboscopy and, in addition, oscillometry was carried out. Speech therapy was carried out for 64 patients and follow-ups were made with electroglottography and the above-mentioned parameters. The methods and preliminary results are discussed.

During recent years we have seen between 20 and 25 patients with paralysis of one or both recurrent nerves per year The patients have been examined in the ENT department, and if possible also by a speech therapist. We give here some information of the results of 96 patients, 70 women and 26 men, examined during the last 4 years.

Fifty two patients had their recurrent nerve alysis after surgery for benign thyroid and parathyroid disorders. 11 patients had no other symptoms. 10 patients had malignant tumours, 7 cases have been diagnosed after influenza, 6 patients had intracranial disease and 4 patients had cardio-vascular disease 1 patient had had a trauma of the thorax, 1 patient had had thoracic sympathectomy performed bilaterally and 1 patient had brachyesophagus and a diverticulum of the esophagus. In 1 patient paralysis probably was due to compression from an enlarged thyroid gland, in 1 patient due to direct trauma and in 1 patient probably due to compression from a pulsating mediastinal tumour

Nine patients had paralysis of both recurrent nerves, 30 patients had right sided paralysis and 57 patients left-sided paralysis. 73 of the 96 patients had the paralysed vocal cord in paramedian position

Phonation time was, on average 8 seconds, the respiration mostly costal. At stroboscopic examination of 53 patients, among other parameters the amplitude was examined. 21 had an increased, 25 a reduced amplitude. 7 had normal amplitude. All had irregular vibration pattern. The voice range was much reduced, the pitch also reduced, on average

The auditory examination and control of treatment by the speech therapist was felt insufficient and an oscillometric description of the tape recordings that were routinely taken was attempted. Among others, Smith (1961) and Lauritzen & Frøkjær Jensen (1970) have tried to evaluate the effect of speech therapy and have found that the sound spectrum over basic pitch frequency is intensified and that noise on voices with paralysis disappears. Among others Kolke (1968) and v Leden & Kolke (1970) have shown that the vibration pattern of the vocal cords in patients with paralysis of the recurrent nerve is irregular

We have tried to evaluate whether these parameters, 1) regular/irregular curve, 2) overtones, and 3) evaluation of noise could give us further information that would be useful in our practical work. This evaluation has till now been done by ourselves without mathe

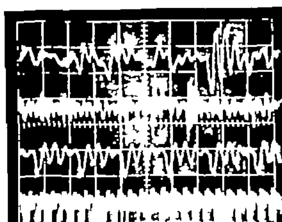


Fig. 1. Oscillometric curves. The upper and the third curve show 5 vibrations of a male with unilateral recurrent nerve paralysis before and after voice therapy. The second and fourth curves show the same voice at higher oscilloscopic speed.

matical calculation. We think that insufficient practical work has been done hitherto, to determine which parameters are most valuable for mathematical calculation.

In Fig. 1 are seen 2 oscillometric recordings, before and after voice treatment. The upper shows an irregular curve lack of overtones and noise. The lower shows regularity in vibration pattern, overtones and a smooth curve without noise.

At a follow-up examination of 47 patients, performed on an average 2 years after the diagnosis was made, 20 patients had persisting unilateral paralysis, 18 had no paralysis, 8 had some movement of the previously paralysed vocal cord and 1 had a persisting bilateral paralysis.

The 20 patients with unilateral paralysis had an average phonation time of 11 seconds, pitch was normalised (215 Hz for women, 115 Hz for men). Voice range was, on average, 19 semitones. The stroboscopic examination was very uncertain, there was some movement of the paralysed cord in all cases except 3.

Apart from the oscillometric examination, electroglottography was also carried out, where we tried to distinguish between 1) long/short closure, 2) identical/nonidentical vibration pattern and 3) even/uneven course.

Our electroglottographic results were not so clear as we had expected. This may be due to our evaluation method, which has to be refined in the direction recently described by Reinsch & Gobsch (1972). We found a rather short closing phase at 10 of 18 patients without paralysis, in 1 of these no oscillometry was done and in 9 of 20 patients with unilateral paralysis. This corresponded to the stroboscopy which showed poor voice function in many of those patients without paralysis. So there was good harmony between the stroboscopy and the electroglottography. The oscillometry was better when it came to the description of differences between patients with and without paralysis, possibly because it could be called a more "summarizing" examination.

Sixty four patients had voice therapy and were all treated after Smith's accent method.

Table I *Oscillometry*

	At time of diagnosis (−16)	After voice therapy when no follow-up	At follow-up persisting paralysis	At follow-up no paralysis
Number of patients	80	32	20	17
Regular vibration pattern	21	22	13	13
Irregular vibration pattern	59	10	7	4
Many overtones	7	14	7	12
Some overtones	14	13	7	4
Lack of overtones	59	5	6	1
– noise	35	24	19	15
noise	45	8	1	2

On average the patients had 15 treatments. We think that the best results are probably obtained after more than 10 treatments of one half-hour each.

We have tried to find some practically usable and simple methods for measuring voice disorders, not only paralysis of the recurrent nerve At the same time we feel that we have got far better evaluation possibilities for voice therapy Our present examination program now comprises indirect laryngoscopy examina tion of pitch and voice range phonation time, respiration, stroboscopy tape recordings, oscillometry and electroglottographic examination.

EQUIPMENT

Stroboscope, Brüel og Kjær type 4910, with frequency analyzer type 2107 and condensor microphone type 4131

Storage oscilloscope, Tektronix, type 564B, model 121N with a polaroid camera.

Tape recordings were performed on an Akai X 360 recorder frequency range 30–20 000 Hz with condensor microphone CM 15 and transferred to the oscilloscope with an UHER 4000 report L, frequency range 40–20 000 Hz.

The electroglottograph was built by B. Frøkjær Jensen after the principle of Fabre.

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VOCAL CORD PARALYSIS TREATED WITH TEFLON IMPLANTATION

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Abstract Nine cases of unilateral vocal cord paralysis with severe hoarseness combined with atrophy of the cord and asymmetry of the larynx were treated with implantation of Teflon in the paralytic vocal cord by Arnold's method. The voice quality was studied and judged by a listener-jury After implantation the range of the voice was widened, the maximum phonation-time was remarkably prolonged and the quality of the voice improved significantly

Training of the voice in cases of unilateral vocal cord paralysis most frequently gives a good result. The mobility of the healthy cord improves, resulting in closure of the ligamentous part of the glottis and the voice of the patient becomes clear Sometimes, however no result can be achieved by training-treatment. This applies to cases where an atrophy of the vocal muscle in the paralytic vocal cord has occurred. If the edges of the cords do not meet on the same level the dysphonia becomes even more difficult to control. In these cases the glottis is not only quite inadequate as a tone-generator but coughing and creating abdominal tension also become more difficult.

Brüning's idea (1911) to inject paraffin into the paralysed vocal cord was in principle excellent, but paraffin had to be replaced with something else which was indifferent and stable. Such a material has been found in Teflon, which is a polymer of tetrafluoroethylene Pulverized Teflon in 50% glycerol suspension gives a paste which is easy to inject into the vocal cord. For this purpose a special injection-pistol developed by Brüning is used. Arnold in particular has published studies on this topic during the years 1955–64

The implantations in the present study have been done according to Arnold's technique (1962). Tomography of the larynx is very helpful when planning the procedure. In the ENT Department of Helsinki University Central Hospital these operations were performed under general anesthesia using Kleinsasser's microlaryngoscopy equipment.

The material comprised 9 extremely hoarse patients. In 5 cases the etiology of the paralysis was a struma-operation. The remaining 4 cases were 2 lesions of the vagus nerve caused by removal of tumour one idiopathic paralysis of the vocal cord, and one patient was injured during the war by a shell fragment in the neck.

Larynx-tomograms were taken during breathing and intonation before and after Teflon implantation, stroboscopy was done and the maximum range of phonation (MFT) was measured. The pitch of the spoken voice and the physiologic tone-range were also measured. Tape recordings were made, and these samples were judged by a listener-jury who classified them in five categories according to the quality of the voice Taking the mean of the judgements, a voice-quality index was obtained. In the statistical handling of the material a paired *T*-test was used (the paired *T*-test of difference, Ipsen & Feigl, 1970).

Common to all the patients before im-

On average, the patients had 15 treatments. We think that the best results are probably obtained after more than 10 treatments of one half-hour each.

We have tried to find some practically usable and simple methods for measuring voice disorders, not only paralysis of the recurrent nerve At the same time we feel that we have got far better evaluation possibilities for voice therapy Our present examination program now comprises indirect laryngoscopy examination of pitch and voice range, phonation time respiration, stroboscopy tape recordings, oscillometry and electroglottographic examination

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WHAT IS PROLONGED INTUBATION?

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Abstract The risk of damage to the upper airways by nasotracheal intubation is influenced not only by its duration, but also by a number of other factors. Among 29 patients treated by nasotracheal intubation, as a rule for 2–3 days, none showed laryngo-tracheal damage after extubation. Among 20 patients intubated for a longer period (5–56 days) numerous cases of damage to the respiratory tract were found. Prolonged intubation should be taken to mean intubation lasting longer than 6–7 days. With prolonged intubation the risk of severe damage to the larynx and trachea is so great that the possibility of replacing it by tracheostomy should be seriously contemplated.

Through the past 20 years oro- and nasotracheal intubation has been gaining ever increasing ground in the treatment of pulmonary insufficiency In Scandinavia this development was triggered by the polio epidemic of 1952 in Copenhagen, when tracheal intubation was performed through tracheostomy (Lassen, 1956) The hazards involved by an oro-nasotracheal tube especially to the larynx and subglottis, were soon realized, and it was generally considered that the tube had to be removed within 12–24 hours (Lewy & Sibbert, 1951 Dam & Zwergius, 1952) As recently as 1962 Bergström recommended removing nasotracheal tubes at the end of 24 hours.

Since that time, opinions have become more liberal, and it was considered justified to continue the intubation for 2 or 3 days (Fearon et al., 1966 Hatch, 1968 Hedden et al., 1969). In Denmark too nasotracheal intubation of an average duration of 2–3 days was reported in a series of patients without deleterious effects (Hansen & Jørgensen, 1968 Träff & Tos, 1969)

In the literature prolonged" intubation is often mentioned without any explanation of what "prolonged" is taken to mean. Many variables play a role in damaging the respiratory tract. The general condition of the patient, the state of consciousness, premorbid respiratory infections and age. The material of the tube, the cuff pressure, and the frequency of changing the tube are also contributory pathogenetic factors.

In the present study it was endeavoured to ascertain for how long nasopharyngeal intubation can be maintained without a risk of clinical damage to the larynx and trachea.

Present investigations

Twenty-nine cases of acute epiglottitis in children were treated with nasotracheal intubation and antibiotics.

The majority were intubated for 2 or 3 days, and after extubation no patient of the entire group exhibited lesions of the larynx or trachea that required treatment. There was merely some hoarseness or stridor for a few days after extubation.

In another series comprising patients with respiratory insufficiency often of complex genesis, the nasopharyngeal intubation was of longer duration.

The primary disease that provided the indication for intubation was pulmonary in 9 whereas 8 patients had cerebral contusion. 3 patients were intubated for various reasons. The patients of this group were in an extremely poor condition, 17 were primarily ı

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Table I *Intubation group I (29 patients)*

Duration of intubation in days.			
<1	1–<2	2–<3	3–<4
8 pts.	14 pts.	5 pts.	2 pts.

Table II *Intubation group II (20 patients)*

Duration of intubation in days.			
5–6	8–12	14–21	>21
3 pts.	11 pts.	3 pts.	3 pts.

11 were treated in a respirator and 3 had cardiac arrest.

Within intubation group II there was clinically demonstrable damage to the larynx and subglottis in practically all patients, although no or negligible damage was found in those who had been intubated for 5 and 6 days. The severity of the laryngo-tracheal damage was to some extent dependent upon the duration of the intubation but this was not a rule without exceptions, as may be seen from Table III.

Among the cases designated + + the vocal cords were found to be immobile in a position of adduction exactly like the appearance of paralysis of the recurrent laryngeal ...re, but being in fact a sequel to fibrous changes in the articular and muscular apparatus of the vocal cords. Since no patient of group I had clinically demonstrable damage in the trachea and since the first 3 patients of group II did not have such damage or at least only very mild laryngo-tracheal changes, it may be concluded that naso-tracheal intubation may be maintained for 6–7 days without major risk of damage. If it is kept up longer it must be called prolonged intubation, which means a considerable risk of severe sequelae in the larynx and subglottis, possibly requiring treatment. In such cases, therefore it must be carefully contemplated whether instead of continuing the risk of prolonged

Table III *Influence of the duration of intubation upon the severity of laryngo-tracheal sequelae*

	Sequelae			Sequelae	
No. of days	lar + subgl.	Trachea	No. of days	lar + subgl.	Trachea
5	0		11	+	
5	+		12	+ +	
6	+		12	+ +	
8	+ +	+	12	+	
8	+ +		14	+ +	
8	+ + +		15	0	
9	+ +		21	+ + +	
10	+ + +		26	+ + +	+
10	+ +	+	30	+ +	
10	+ +	+	56	+ + +	

\+ Mild mucosal thickenings, granulation tissue.
\+ + Permanent, considerable stenosis of the lumen of firm, fibrous nature.
\+ + + Anatomical structures in the larynx are destroyed, larynx funnel-shaped, a few mm passage to a greatly narrowed subglottis.

intubation it is not advisable to replace it by intubation through tracheostomy

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TREATMENT OF ACUTE EPIGLOTTITIS IN CHILDREN BY LONG-TERM INTUBATION

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Abstract A description of the treatment of children with acute epiglottitis by long-term intubation is given. The results of treating 39 children by intubation are compared with the results of treating 51 children by tracheostomy

Endotracheal intubation is now accepted as an alternative to tracheostomy in the treatment of acute epiglottitis. From November 1969 to November 1971 at the Central Hospital in Västerås, 39 children with acute epiglottitis were treated by endotracheal intubation. In this lecture we present our experiences with this method and compare it with 51 epiglottitis children treated by tracheostomy during the time 1962 to October 1969 During the whole of this period there was a total of 116 cases of which 51 were tracheostomized, 39 treated with intubation and the remaining 26 received only medical treatment.

There has been a successive increase in the number of epiglottitis cases per year (Fig. 1) Of the 90 cases who had been either tracheostomized or intubated 38 were girls and 52 boys. Age distribution is shown in Fig. 2. 79% of the patients are in the age group 2–6 years. All the patients, both tracheostomized and intubated, have received antibiotics and steroids, first by injection and afterwards orally Large doses of Hydrocortisone were given up to approx. 1 gram on the first day Afterwards Prednisolone in decreasing doses was given. Average hospitalization for tracheostomized patients: 6.5 days, average time with tracheostomy 2.7 days. Average hospitalization for intubated patients 3.9 days, average time with tube, 1.5 days.

The longest time with a tracheostomy cannula was 6 days and the shortest, 1 day The longest time with a tube, 2.5 days and the shortest, $^1/_2$ day

Complications

We have had very few serious complications in association with tracheostomy No deaths have occurred. All the tracheostomies were carried out under intubation anaesthesia. The complications we have had appear in Table I and from this it can be seen that in 17 of the 51 tracheostomized cases, 39% some form of complication occurred. Serious complications have only occurred, however in 2 cases, namely the bilateral pneumothorax and the granuloma in the trachea. In the first of these the intubation was extremely difficult and the anaesthetist never managed to get the tube past the vocal cords and the tracheostomy must be regarded as an emergency procedure. In the second case, with stridor approx. 1 month after tracheostomy direct laryngoscopy revealed a granuloma the size of a pea on the anterior wall of the trachea. Since this was removed the patient has been free of symptoms.

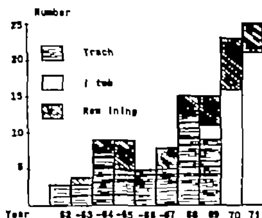


Fig 1 Number of children with acute epiglottitis per year from January 1962 to November 1971

In the 39 intubated cases no serious complications occurred as can be seen from Table II. There was, however some form of minor complication in 15% of the cases. Among the 39 cases of intubation 1 death occurred which, however had nothing to do with the method as the patient had already suffered a cardiac arrest before he was intubated.

Follow up

The intubated patients have been controlled after approx. 2 weeks by an indirect laryngoscopy and 34 of the 39 cases have been studied by direct laryngoscopy under anaesthesia between 1 and 11 months after the intubation treatment. In none of these cases was any remaining abnormality found in the epiglottis, larynx, or subglottically

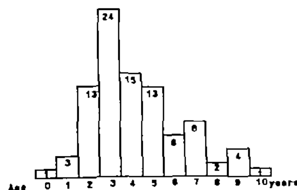


Fig 2 Age-frequency (90 patients).

Table I *Complications with tracheostomy*

1	Bilateral pneumothorax	1 case
2	Mediastinal emphysema	2 cases
3	Subcutaneous emphysema	3 cases
4	Small incision of posterior wall of trachea	1 case
5	Patient decannulated himself	1 case
6	Granuloma in trachea	1 case
7	Stridor and tendency to stenosis 1–2 months after tracheostomy	1 case
8	Disfiguring scars	7 cases

Total number of complications in 51 tracheostomized patients. 17

Details of technique

We feel that it is very important to lay advance plans for intubation treatment It is obvious that good cooperation must exist between the departments of anaesthesia and E.N T During the time we intubate the child we have always an E.N T surgeon ready to do a tracheostomy if necessary After the intubation an X-ray is taken immediately on the operation table. The child is anaesthetised with oxygen followed by N_2O/O_2/fluothane and intubated without the help of muscle relaxants. Intubation is carried out first orally in order to judge the size of the tube and a tube is then selected for nasal intubation 0.5 or 1.0 mm smaller than that which easily passes through the larynx. It is important to stress that the tube should be as small as possible, without producing any respiratory obstruction. One of the big problems is sedation of the child. For this we use large doses of Diazepam which we give intravenously before the child is awake. We treat the child in an ultrasonically humidified tent and it is important to stress that the

Table II *Complications with intubation*

1	Coughed up tube	1 case
2	Extubated himself	1 case
3	Rapidly resolving atelectasis of the right upper lobe due to the tube being too far down	4 cases

Total number of complications in 39 intubated patients: 6

humidification must be perfect with these small tubes. The tubes are made from poly vinyl chloride, manufactured by Portex.

CONCLUSION

We believe that intubation treatment has obvious advantages over tracheostomy for the treatment of acute epiglottitis in children, for the following reasons:

1 It eliminates the risks for pneumothorax, mediastinal emphysema, subcutaneous emphysema etc. together with the other complications of tracheostomy

2. It decreases risk for tracheal stenosis.

3 It avoids unsightly scars in the throat.

4. It reduces the period of hospitalisation, in this study on an average from 6.5 to 4 days.

5 Problems with decannulation, especially with small children, disappear

Intubation has also some disadvantages. There is a risk of damage to the larynx and trachea. This would seem to be very small in acute epiglottitis as the child is intubated for a short time only We do not use a cuffed tube and no respirator is necessary It is also important to stress that the tube should be as small as possible. It is somewhat more difficult to suck out the lungs through a small tube but with some experience this is by no means impossible. It is necessary to have good monitoring of the children and they are most suitably treated on an intensive ward with availability of an E.N T and an anaesthetic specialist.

Since this material was collected 10 further cases of acute epiglottitis have been treated in Västerås of which 7 required intubation. 4 of these have been directly laryngoscoped and found to be quite normal afterwards. The total of intubation treated patients is now 47 of which 38 have been checked afterwards.

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NASOTRACHEAL INTUBATION INSTEAD OF TRACHEOTOMY IN ACUTE EPIGLOTTITIS IN CHILDREN

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Abstract 30 children with typical, severe, acute epiglottitis were treated by intubation of 8–192 hours duration, mean 42 hours, instead of by tracheotomy The method, results, and combinations of intubation are described. The results were good, complications few and negligible, and no damage to the larynx occurred. Since all children have to be intubated anyway in order to be tracheotomized, and since the critical period of airway obstruction lasts a maximum of 48 hours, the tube may just as well be left and tracheotomy avoided.

In acute epiglottitis immediate measures are often needed to secure the respiration. This was previously done by tracheotomy In 1965 [illegible] was introduced in the Gentofte [illegible] (Buchmann & Riskær 1967) and in [illegible]67 in the Glostrup Hospital (Träff & Tos, 1969). Since then tracheotomy has not been used in acute epiglottitis in these two hospitals. The material from Gentofte counts 10 cases, that from Glostrup 20 intubated children with typical, severe acute epiglottitis.

The youngest child was 1 year of age, the oldest 12. 17 were under 2 years, 7 between 3 and 4 The duration of symptoms before admission was more than 24 hours in only one case (Table I), that of respiratory embarrassment in most cases 2–6 hours. Many children were admitted in an extremely poor condition 7 with distinct cyanosis. 17 had to be intubated immediately (Table I)

Twenty-five children had nasotracheal intubation, 5 orotracheal under general anaesthesia using smooth polvinyl chloride tubes. The intubation was done in the operating theatre of the E.N T Dept. with readiness for tracheotomy and bronchoscopy As a rule it could be carried out at first attempt. By McIntosh laryngoscope and the tube the epiglottis was pressed forward. The posterior edge of the arytenoid region was then visible, and the tube could be passed. The tubes were as thin as possible so as not to irritate the vocal cords and from the outset allow respiration outside the tube The patients were placed in an Air Shield croupette. The object was to extubate as soon as possible, even though oedema of the epiglottis remained. The critical period of acute epiglottitis is the first 24 hours there after the oedema starts subsiding. The intubation lasted in most cases for 25–36, mean 42, hours (Table I). Two patients could be extubated after 8 hours, one was intubated for 192 hours. This latter patient had acute epiglottitis, but also subglottic laryngitis. After 72 hours' intubation extubation was tried, but the patient had to be re-intubated for 48 and thereafter again for 72 hours.

Complications and symptoms following extubation were few and negligible Constant stridor was observed in 7 cases, lasting for 1–2 hours in three and for 3–6 hours in three Only one patient had mild, constant stridor for 24 hours. This patient had been intubated for 48 hours. In 5 patients there was inter

Table I *Duration of symptoms and of respiratory embarrassment before admission. Time of intubation after admission and duration of intubation in hours*

	Number of patients in each time interval											Mean time in hours
	Immediately	Time intervals in hours										
		1	2–3	4–6	7–12	13–24	25–36	37–48	60–67	83	197	
Duration of symptoms				3	11	15		1				16
Duration of respiratory embarrassment			8	17	2	3						6
Time of intubation	17	5	5	1	[illegible]							1
Duration of intubation					2	4	10	8	4	1	1	42

mittent stridor mainly during sleep, as a rule for 24 hours, but in one case for 4 days. Stridor following extubation was due to the still swollen epiglottis, hardly to oedema of the vocal cords or of the subglottis, caused by the intubation. The mean intubation period in patients with stridor had been 41 hours, in those without 43 hours.

Hoarseness was found after extubation in 9 cases, in 2 of them for 3 and 8 days respectively. Both had been intubated for only 24 hours. In the remaining 7 cases the hoarseness lasted 1–48 hours. Hoarseness following extubation must be due to oedema of the vocal cords caused by the tube. The mean intubation period in patients with hoarseness was 59 hours, without hoarseness 35 hours. The Glostrup series was examined 1–4 weeks and the Gentofte series 1–12 months after discharge. In all cases the vocal cords and voice were normal.

During energetic antibiotic therapy the Gentofte series, but not the Glostrup series, was treated with Actocortin. The mean intubation period in 10 Actocortin-treated children was 48 hours, in 20 non-Actocortin-treated ones 39 hours. The time it took the epiglottis to become normal was 6 days in both series. Actocortin is hardly necessary and presumably has no convincing effect upon the normalization of the epiglottis. At least intubation should not be delayed while waiting for the questionable and slow effect of Actocortin, as the respiratory embarrassment may very rapidly get worse.

Prolonged intubation is, and should still be feared by otologists because of its damage to the larynx. Severe laryngeal damage is often reported following prolonged intubation. However it is difficult to define what prolonged intubation is, as this does not depend only upon the intubation period, but also on many other factors. Nasotracheal intubation as administered in the present material, can hardly be considered prolonged intubation, and possesses several advantages above tracheotomy: (1) Children are in a very poor condition, and the airway has to be secured immediately. This can only be done sufficiently well by intubation. (2) Even though the child has been intubated, it is still very ill, so that acute tracheotomy with its well-known complications during and after the operation, especially common in children, is not indicated. (3) Extubation problems are less serious than decannulation problems. (4) The psychic trauma is not greater in intubated than in tracheotomized children.

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TREATMENT OF STENOSIS OF THE TRACHEA

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Abstract A closed tubulation-technique is described for the treatment of patients with stenosis of the trachea. The results of treatment in 29 patients with stenosis of the trachea—induced mainly by prolonged intubation—are reported.

The operation is performed through an external incision. A tube of silicone is enclosed in the trachea and sutured to the tracheal wall. In this way normal respiration through the upper respiratory tract is possible. In 22 patients this treatment was a success. In 7 patients the tube had to be removed because of respiratory failure and stagnation of secretion.

The method seems to be suitable in all patients with stenosis and malacia of the trachea except in patients with respiratory failure and stagnation of secretion. A transverse resection may be preferable in stenosis of limited size in the upper trachea.

This paper will be published in its entirety elsewhere.

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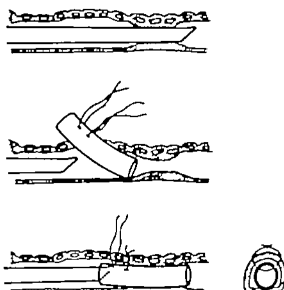


Fig 1 Schematic drawing of the procedure. (*Upper*) ventilating bronchoscope introduced through the stenosis of the trachea. (*Centre*) insertion of the tube. (*Lower*) tube in position. (*Right*) transversal section of the trachea with tube in position, showing suture.

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ANAESTHESIA IN OPERATIONS FOR LARYNGEAL AND TRACHEAL STENOSIS

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Abstract. The authors describe anaesthesia methods in 61 operations for the correction of laryngeal and/or tracheal stenosis. Methoxyflurane (Penthrane®) with large doses of clobutinol chloride (Silomat®) and diazepam was found to be the most practical and was the anaesthesia mainly used.

Since 1966, 61 operations for the correction of laryngeal and/or tracheal stenosis have been performed in the Helsinki University Otolaryngological Hospital. The technique of these operations was previously described in detail by Grahne (1971) and by Grahne & Poppius (1972) The permanent chronic stenoses can be found on three different levels: in the larynx, in the cervical and in the thoracic trachea.

Prostheses according to Aboulker (1962, 1968) and Aboulker et al. (1966) and Aubry & Bourdon (1960) were used. At the very beginning of the series a prosthesis according to Clerici also was tried. At first we had difficulties in finding a convenient method for anaesthesia.

Choice of anaesthesia

There were several problems. It was important not to reduce the already narrow airway with an endotracheal tube. It was also necessary to maintain the spontaneous respiration of the patient during various phases of the operation. In the laryngeal stenosis cases we could by pass the constricted area by performing a tracheotomy and inserting an endotracheal tube below the stenosis.

In the operations of the cervical and intrathoracic trachea we encountered much greater problems. In these cases there was no room for an endotracheal tube. We had to find some other practicable method of anaesthesia to supplement the effect of the premedication and *local infiltration anaesthesia.*

The anaesthesia methods in the various operations are shown in Table I. At first we used a combined nitrous-oxide halothane anaesthesia. This combination however did not permit the use of vasoconstricting agents in connection with the necessary local anaesthesia. The patient had to breath spontaneously on several occasions because there was no room for the endotracheal tube or for artificial ventilation.

Next choice was methoxyflurane (Penthrane®) a long-lasting anaesthetic which preserves the spontaneous respiration even in deep levels of surgical anaesthesia. Penthrane also has fewer side effects than halothane when administered simultaneously with vasoconstrictors.

Many problems were caused by the great sensitivity of the endolaryngeal and particularly of the subglottic region with the subsequent strong cough reflex. This cough reflex could not be controlled with halothane or methoxyflurane. Muscle relaxants could not

Table I *Anaesthesia in operations for tracheal and/or laryngeal stenosis*

	Anaesthetic						
Operation	Local	Sil-Dzp	Sil-Dzp +other	Other i.v	Hal.	Mof	Σ
Cherici	3	—	—	1	11	—	15
Aubry	1	2	2	2	2	3	12
Aboulker	3	5	6	6	2	7	29
Intrathor	1	2	—	2	—	—	5
Σ	8	9	8	11	15	10	61

be used to any great extent because of the occasional need for spontaneous respiration. The primary operation was always begun with a tracheotomy which already indicated seda tion.

We then administered diazepam intrave nously with a total dosage of 10–70 mg, which already gave a very satisfactory sedation. How ever diazepam did not help beyond the tracheotomy mostly performed under local anaesthesia, because the posterior wall of the larynx needs a much stronger anaesthesia. Nor was diazepam capable of elminating cough reflexes during the operation in the endolarynx.

During the postoperative phase of previous laryngeal and tracheal operations we had ob- ed the very good effect of clobutinol ilorlde (Silomat®) in controlling the cough reflex. The dose of clobutinol chloride, how ever was much larger than that needed in most diseases with cough symptoms. Our doses varied between 20–80 mg given in inter mittent i.v injections of 5–10 mg. We found that clobutinol chloride, even when given simultaneously with diazepam reduced the cough reflex very effectively without depressing the respiration. In those cases where the respiration was secured by an endolaryngeal tube we were able to supplement the anaesthesia by using methoxyflurane or a muscle relaxant. These drugs could not be used, when it was necessary to have good spontaneous *breathing during the operation* within the trachea and during the positioning of the prosthesis.

After the Aboulker prosthesis had been placed in position, the height of its upper end was checked by direct laryngoscopy carried out by the anaesthetist. When the Aboulker prosthesis was correctly placed, anaesthesia was continued through the silver cannula until the end of the operation. Diazepam–Silomat combination was also very effective for the final control laryngoscopy

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EXPERIMENTAL TRACHEAL WALL INJURY

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Abstract. A plan for experimental analysis of tracheal wall injuries in rabbits is presented. Preliminary results after different types of injuries to the tracheal mucosae are given.

During recent decades the problem of tracheal wall injury has been discussed in several clinical and experimental investigations (Ekedahl & Lange Hellman, 1967 Harrison & Tonkin, 1966 1968 Lindholm, 1969· Miller & Sethi, 1970· Hilding, 1971) None of these papers have, however solved the fundamental problem of the effects of different parameters such as wall pressure, intubation time, size of tube, etc., on the tracheal wall. It must be assumed that these factors, either in isolation or together may cause irreversible changes in various wall structures.

Against this background we have tried to analyse the degree of tissue injury from different points of view Fig. 1 is a schematic representation of the methods used in this study

Lesions of the tracheal wall in rabbits have been induced experimentally under defined conditions and analysed morphologically according to a method described by Björkerud (1969 1972). The types of injury induced were superficial with either small or large surface area. The animals were sacrificed after intervals varying between 24 hours and 4 weeks. Numerous leucocytes and goblet cells were present in and near the damaged zone 1 week after the trauma. Ciliated epithelial cells were found in uninjurd parts of the trachea but absent in the injured region. Three weeks after the trauma tortuous capillaries with varying diameters, monocytes, and focal necrotic areas were found. Characteristic features of the necrotic areas were a central elevated region with necrotic cells and leucocytes. Both the necrotic and the immediately surrounding zone were devoid of epithelium. Thus, a very small trauma to the tracheal mucosa is followed by such protracted changes as subchronic inflammation, focal areas with necrosis, and incomplete regeneration of the epithelium. Further studies are needed to elucidate the repair capacity of the tracheal wall in more detail and which factors may promote or prevent the repair of the tissue.

The tracheal vascular bed has been visualized by means of intra-arterial perfusion of Indian ink in non-intubated and intubated rabbits. The intubation time has been 90 minutes. The wall pressure used in this study was 20 mmHg (to be published) The normal architecture of the vascular bed in the rabbit is dominated by the venous plexa situated in the submucosa between the cartilage rings. These plexa are connected by arcades of vessels crossing the rings. There is also a very fine net of blood vessels in the mucosa. In microangiograms from rabbits sacrificed with the cuffed tube still in the trachea, most of the vessels are blocked and only a few arterioles are found in the submucosa. In the animals sacrificed 40 minutes after extubation an almost normal architecture of the

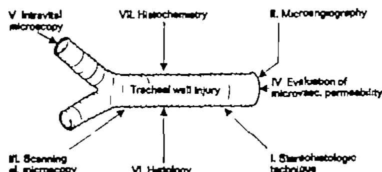


Fig 1 Schematic representation of the methods.

arterioles and venoles was found. The microvessels in the mucosa were poorly filled, however These findings indicate vascular injury to the capillary network.

Only preliminary results with a few methods are here discussed. Other ways of attacking these problems (as was indicated in the figure) are presently being studied. We hope that further studies along these lines will clarify the mode of reaction of this tissue.

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EXPERIENCE WITH A NEW OROTRACHEAL TUBE

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Abstract. A preshaped tube which conforms to the contour of the airway exerts less pressure against the posterior wall of the larynx than a conventional tube. Clinical evidence is presented which shows that lesions in the posterior part of the larynx are significantly less pronounced following prolonged orotracheal intubation with preshaped tubes than with conventional tubes.

Without exception, observations have shown that conventional straight or slightly curved oro- or nasotracheal tubes exert a considerable pressure against the posterior wall of the larynx and the anterior wall of the trachea. The shape of a conventional tube is far from ideal and when it is reshaped according to the anatomical structures, when introduced into a patient, it gives rise to undue pressure necrosis and ulcerations. It is to be expected that these kinds of lesions can be avoided or greatly reduced if a preshaped tube is used. A tube which conforms to the airway is now available and is manufactured by Portex Ltd. (Fig. 1).

A comparison has been made between 69 adult patients (Series I) treated with indwelling conventional orotracheal tubes for >24 hours (mean 32 hrs) and 45 adult patients (Series II) treated with indwelling preshaped orotracheal tubes for >24 hours (mean 44 hrs). Both groups were otherwise treated in the same manner in the same intensive care units, and by the same staff. All patients were carefully examined by repeated indirect or direct laryngoscopies following the period of intubation. Acute damage in the larynx was classified according to previously described principles (*Acta Anaesth Scand* Suppl. *33* p 53). The results are given in Table I.

The lesions healed within 15 days in 23% of the patients in Series I and in 60% in Series II within 30 days in 65% in Series I and in 91% in Series II. Delayed healing with associated granuloma formation occurred in 33% in Series I and in 9% in Series II and healing times longer than 30 days occurred in all of these patients.

No voice changes or voice changes lasting less than 1 week were noted by 66% of the patients in Series I and by 74% in Series II changes lasting from 1 to 3 weeks were noted by 16% of the patients in Series I and by 17% in Series II. Voice changes lasting 1 month or more were reported by 18% of the patients in Series I and by 9% in Series II.

Airway obstruction in the larynx following extubation was observed in 1 patient in Series I. No such difficulties were experienced by patients in Series II.

The carina to tube distance was measured in routine chest radiographs. In women this distance varied between 2.7 and 5 cm (mean 3.3 cm) in men between 2 and 5.4 cm (mean 4.1 cm). These figures are valid for the recommended tube sizes, e.g. in women 7.5 mm ID in men 8.0 or 8.5 mm ID.

This investigation confirms that lesions in the posterior part of the larynx are significantly less pronounced when preshaped orotracheal tubes are used instead of conventionally shaped tubes.

In my opinion it is desirable to use a pre-

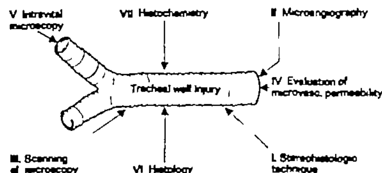


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CUFF PRESSURE AT ENDOTRACHEAL INTUBATION

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Abstract. A preliminary investigation on the tracheal wall pressure from endotracheal tube cuffs is reported. A simple technique for calculation of tracheal wall pressure is presented. A limited clinical material has been analysed regarding cuff inflation volume, cuff pressure and resulting wall pressure.

It is well known that cuffed endotracheal tubes can produce varying degrees of local tissue damage (Adriani & Phillips, 1957 Cooper & Grillo 1969· Hilding, 1971)

As a background to further experimental studies on tissue injury produced by such cuffs the pressure load on the tracheal wall has been analysed. Various methods have been devised giving a direct or indirect measurement of the actual wall pressure (Adriani & Phillips, 1957 Carrol et al. 1969· Hilding, 1971 Knowlson & Basset, 1970). All of these methods include some kind of arrangement either on the tube or in the tracheal wall.

One of the main aims of the present study was to evaluate the pressure load at routine use of cuffed rubber tubes (Rüsch). A method was therefore required that could be used without previous information to the staff working daily with induction of anaesthesia and intubation.

By measuring the actual cuff inflation volume and pressure with the tube in the trachea and the corresponding volume and pressure situation with the free tube it is possible to obtain a fairly accurate value of the lateral pressure caused by the cuff This hypothesis was tested and also confirmed in model experiments on autopsy material.

Fig. 1 shows the increasing cuff pressure with successive inflation of the intratracheal cuff and of the free cuff The calculated resulting wall pressure is given on the abscissa. The steep rise in the later part of the wall pressure curve is important to emphasize.

The same method can be used to elucidate minimum occlusive volume (MOV) and corresponding minimum occlusive wall pressure (MOWP) for different intratracheal pressures. Theoretically minimum occlusive wall pressure should equal or just exceed the intratracheal pressure (Adriani & Phillips, 1957 Knowlson & Basset, 1970)

Fig. 2 shows the result of measurements on minimum occlusive wall pressure for two tube dimensions in the same cadaver trachea. With this set-up the necessary wall pressure exceeds the intratracheal pressure with about 10 mmHg. A pronounced difference in total cuff pressure is not reflected in the calculated wall pressure. The minimum occlusive wall pressure is compared with an expected arteriolar pressure of 40 mmHg.

With this "calculated wall pressure technique" a limited clinical material has been analysed. Fig. 3 shows the registered total cuff pressures and the resulting calculated wall pressures. It is obvious that routine intubation

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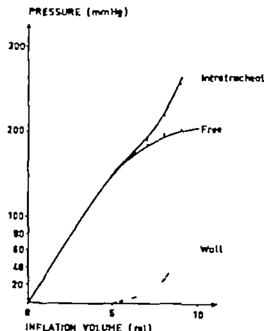


Fig 1 Cuff pressure-volume relation for the free and the intratracheal cuff and the resulting wall pressure

results in a high intracuff pressure with a great variability It should be emphasized, however that there is no direct correlation between this total cuff pressure and the resulting wall pressure nor is there a direct correlation between the cuff inflation volume and the wall pressure.

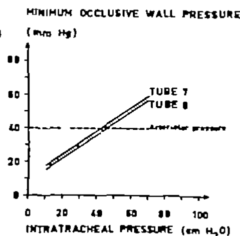


Fig 2 Relation between the minimum occlusive wall pressure and the tracheal pressure for two tube dimensions in an experimental model.

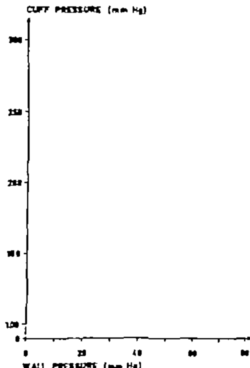


Fig 3 Total cuff pressure and calculated wall pressure in a clinical material.

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INTERACTION BETWEEN THE UTRICLES AND THE HORIZONTAL SEMICIRCULAR CANALS

II. *Unilateral Selective Section of the Horizontal Ampullar and the Utricular Nerve followed by Tilting around the Longitudinal Axis*

E. Fluur and J. Siegborn

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Abstract. Selective unilateral section of the horizontal ampullar nerve and the utricular nerve was performed. By tilting the animals around their longitudinal axis, the alterations in the horizontal nystagmus were studied. It was shown that these alterations were released from the intact utricle. An increase in utricular activity due to tilting toward the operated ear resulted in a positive triggering of the nystagmus from the ipsilateral horizontal semicircular canal. A decrease in its activity by tilting toward the nonoperated ear inhibited the nystagmus. The cause of these findings is discussed.

In a previous article (1972) the authors have shown that tilting of an animal around its longitudinal axis, after selective unilateral section of the horizontal ampullar nerve, results in a characteristic alteration in the frequency of nystagmus. Tilting toward the operated side increased the frequency and tilting toward the nonoperated side caused inhibition of nystagmus. This has resulted in two questions which will be studied in this paper:

1. Does the alteration in nystagmus depend on variation of activity in the utricle?
2. If so, what effect has the utricle on the ipsilateral horizontal semicircular canal?

MATERIAL AND METHOD

Sixty-two adult cats were used for the experiments. The operation, stimulation, and recording techniques are the same as those described in a previous article.

RESULT

All the cats were first subjected to selective unilateral section of the horizontal ampullar nerve, and manifested nystagmus toward the contralateral side. This nystagmus did not change perceptibly when the utricular nerve was also cut. If the animals were tilted toward the operated side 41 of them showed an increase in nystagmus frequency, often from about 17 up to 31 beats/10 seconds. If the nystagmus had previously been somewhat irregular in shape, it now became much more regular as regards both frequency and amplitude. If instead the cats were tilted toward the nonoperated side we found in all of them alterations in nystagmus. In 48 cases there was a total inhibition of nystagmus, which occurred either immediately (12 cases) or slowly after 10–20 seconds (7 cases) with a continuous fall in frequency. Initially 29 cats showed an increase in the frequency of nystagmus, with 5–14 beats/10 seconds, later followed by total inhibition (Fig. 1). Fourteen animals had also an initial increase in frequency from about 17 up to 41 beats/10 seconds, while the amplitude decreased continuously from 2–3 cm down to 1–2 mm, however without total inhibition of nystagmus. Thirty-six cats showed an "ideal" reaction when tilted in either direction, i.e. facilitation during tilting toward the operated ear and inhibition toward the nonoperated side.

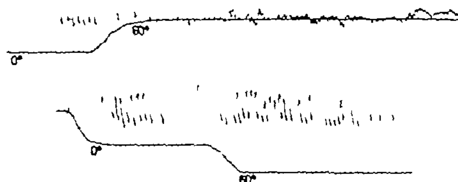


Fig. 1. Consecutive curves from a cat after selective unilateral section of the left horizontal ampullar nerve and the left utricular nerve. The upper curve shows the electronystagmography and the lower curve the tilting of the table. Tilting to the right upwards, to the left downwards.

DISCUSSION

We have created a system with only the hori zontal semicircular canal and the utricle on one side intact (Fig. 2). It has been clearly demonstrated that variations in the discharge frequency of the intact utricle caused by tilt ing, influence the ipsilateral horizontal semicircular canal or its reflex arc. An increase in utricular activity which occurs during tilting toward the operated ear is consequently trig gering the reflex positively for ipsilateral nystagmus (Fig. 3). This also explains the findings (Fluur & Mellström, 1970) electrical stimulation of the midlateral lar area can result in ipsilateral horizontal nystagmus, without this being a result of the current spreading through the endo-perilymph to the horizontal ampulla or its nerve. Consequently every depolarization of this utricular area, whatever its cause, facilitates the activity of the ipsilateral horizontal canal or its reflex arc.

On the other hand, a decrease in the activ ity in the intact utricle which happens during tilting toward the nonoperated side causes a definite inhibition of nystagmus (Fig. 4). In analogy with the argumentation referred to above is this finding due to the fact that a decreased utricular activity lowers the triggering of the horizontal nystagmus down to complete inhibition. These results correspond to similar findings in labyrinthectomized rabbits by Jongkees & Philipszoon (1964).

This inhibition can evidently develop in dif ferent ways, either directly or via an initial increase in frequency. How this is brought about is not known. It may be through direct anatomical anastomosis between the utricle and the horizontal semicircular canal found by Owada et al. (1960) but there are also signs indicating that it takes place all the way up in the oculomotor system being a result of the integrating activity in this system described by Yamanaka & Bach-y-Rita (1968, 1970). The activity of the reticular formation and the wakefulness of the cats are certainly also of great importance.

ZUSAMMENFASSUNG

Selektive unilaterale Abschneidungen der N. ampullaris canalis horizontalis und N. utricularis wurden vorgenommen. Durch Kippung der Tiere um ihre longitudinale Achse wurden die Veränderungen des horizontalen Nystagmus studiert. Es wurde gezeigt, dass diese Veränderungen vom intakten Utriculus ausgelöst werden. Eine Erhöhung seiner Aktivität durch die Kippung in Richtung des operierten Ohres ergab eine Steigerung der Nystagmusgeschwindigkeit, ausgelöst vom ipsilateralen horizontalen Bogengang. Eine Herabsetzung der Aktivität durch Kippung in Richtung des nicht operierten Ohres ergab eine Inhibition des Nystagmus. Der Grund dafür wurde diskutiert.

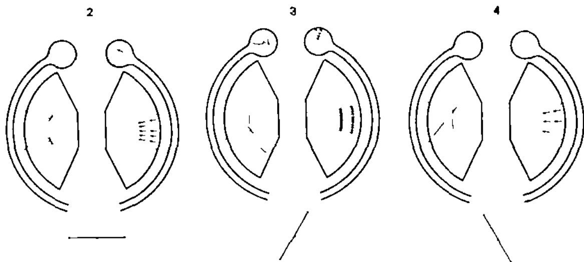


Fig 2 Schematic picture of the utricles and horizontal semicircular canals in horizontal position after section of the left horizontal ampullar nerve and left utricular nerve. The arrows indicate the orientation of the hair cells, i.e., the direction in which they increase their discharge frequency. The number of arrows symbolizes discharge frequency. The line below the picture symbolizes the direction of tilting.

Fig 3 Schematic picture of the utricles and horizontal semicircular canals after unilateral selective section of the left horizontal ampullar nerve and the left utricular nerve, and when the animal is tilted to the left. Arrow indication same as in Fig. 2. The number of arrows symbolizes discharge frequency. The line below the picture symbolizes the direction of tilting.

Fig 4 Schematic picture of the utricles and horizontal semicircular canals after unilateral selective section of the left horizontal ampullar nerve and the left utricular nerve, and when the animal is tilted to the right. Arrow indication same as in Fig. 2. The number of arrows symbolizes discharge frequency. The line below the picture symbolizes the direction of tilting.

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THE ROLE OF THE PERILYMPH IN SEMICIRCULAR CANAL STIMULATION

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(Received June 21 1972)

Abstract The assumption of a mechanical function of the perilymph in vestibular reactions has been reiterated in the literature (Anliker M & v Buskirk, W 1971 The role of the perilymph in response of the semicircular canals to angular acceleration. *Acta Otolaryng* (Stockh.) 72 93). This assumption is essentially based on three premises: that the perilymph should meet a lower resistance than the endolymph because of the larger perilymphatic space, that the ampulla blocks perilymph movement by presenting one wall perpendicularly placed at the end of the perilymphatic canal and that this ampullary wall and the perilymphatic meshwork of loose connective tissue *offer no resistance to perilymph movement*. This paper presents criticisms of each of these premises and maintains that the assumption of a mechanical function for the perilymph cannot be supported or sustained by reference to them.

The assumption that the perilymph may play a role in the physiological stimulation of the sensory epithelium of the cristae ampullaris is not new and has appeared occasionally in several publications and discussions. It might be argued that a structure like the loose connective tissue of the perilymphatic space, which is found in all higher animal species, might therefore be assumed to have a specific and perhaps an important function However the discovery of the significance of the diffusion of water and electrolyte ions through the membranous walls of the inner ear for the equalization of osmotic pressure in endolymph and perilymph might logically seem to be a satisfactory explanation for the presence of perilymph. The chemical constitution of this fluid is a result of ultrafiltration of water and ions from the blood vessels and corresponds to that of other extracellular fluids.

This low viscosity fluid is *not* however a freely movable fluid within the bony walls of the vestibular labyrinth. It is well known since the investigations by de Burlet (1921) that a relatively dense vascularized network of connective tissue turns the vestibular perilymphatic space into a spongy meshwork of varying density which must present an obstacle to the free flow of perilymph. In the cochlear perilymphatic scalae and in the vestibular cisterna surrounding the sacculus there are no such obstacles to an unimpeded perilymph movement. This arrangement is necessary in these regions for the transmission of soundwaves (de Burlet, 1921) This absence or presence of the meshwork of loose perilymphatic connective tissue is the important physical difference between the nature of the perilymphatic space in the vestibular part and that of the cochlear saccular part. These regions of the inner ear are separated by an incomplete dividing membrane, *Membrana limitans* (de Burlet, 1921)

The assumption of a mechanical function of the perilymph in vestibular reactions was first proposed by Reijto (1939) and later reiterated by Anliker & v Buskirk (1971) These

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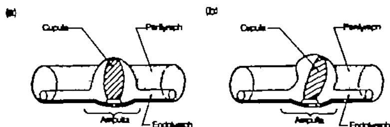


Fig. 1 (a, b) Conjecture of Anliker & v. Buskirk (1971) as to possible mechanics of cupular deflection. *The ampulla is considered to block perilymph* movement by presenting one wall perpendicularly placed at the end of th perilymphatic canal, as in (*a*). (*b*) The resulting cupular movement due to the *presumed perilymphatic flow*

latter authors essentially based their work on the following premises:

(1) Due to the larger size of the perilymphatic space, the perilymph should meet a much lower resistance from the effect of viscosity than the endolymph would experience in the narrow membranous canals.

(2) It was further assumed that the ampulla blocks the perilymph movement by presenting one wall perpendicularly placed at the end of the perilymphatic canal. The cross-sectional area of this wall is assumed to be approximately equal to the cross-sectional area of the ampulla (Fig. 1).

(3) It was also conjectured that the perilymphatic meshwork as well as the ampullary wall should offer no resistance to perilymph movement. The indentation of the wall which should then result from perilymph movement was assumed to cause the cupula to bend and to stimulate the hair cells.

Comments on the First Premise of Anliker and v. Buskirk

To support their statement regarding the difference in cross-sectional area between the endolymphatic canal and the surrounding perilymphatic space these authors reproduce a picture from *Gray's Anatomy*. As scientific support for a theory which greatly deviates from generally accepted viewpoints, its acceptance is questionable.

It must be assumed that these authors would not except their calculations to be valid only for the human vestibular apparatus. The conditions of the perilymphatic space is especially difficult to assess in this species due to the impossibility of acquiring temporal bone fixation without the postmortal changes that easily damage this tissue and also due to the frequent distortions by gas bubbles which develop during decalcification of the thick and dense human labyrinthine bone. It is presumed therefore that the results of Anliker and v. Buskirk are meant to be applicable also to other animal species which have a perilymphatic and endolymphatic system like that of man. The perilymphatic tissue appears to be very thin in humans for the reasons mentioned, and even in other species the real density of this tissue might not be adequately realized without special methods for its demonstration.

Further, it appears that these authors have not made any corrections of their value of the cross-sectional area of the perilymphatic space due to its specific configuration. This area is not a circular or ellipsoidal area as they have depicted their concept. The discrepancy between this hypothetical assumption and the cross-sectional area as it appears in reality is illustrated in Fig. 3 *a*, drawn from the measurements obtained from the pigeon's horizontal canal in Fig. 2. This drawing represents a cross-section through the endolymphatic and perilymphatic spaces for the purposes of estimating the friction these spaces provide to the fluid contained therein. To

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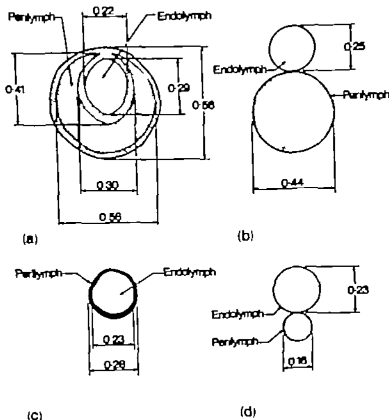


Fig. 3. Drawings of cross-sections through the horizontal canals of various animals. (*a*) A drawing of the pigeon's canal taken from Fig. 2; it shows the relative dimensions of the endolymphatic and perilymphatic lumens. (*b*) The conjecture of Anliker & v. Buskirk (1971) as to the orientation of these two spaces in the pigeon. (*c*) Represents the actual situation in a cat and it is seen that the perilymph is a thin ring around the endolymph. (*d*) Represents the associated model of Anliker & v. Buskirk (1971) relative to the situation for the cat. It is clear from (*b*) and (*d*) that the Anliker & v. Buskirk model of the endolymph-perilymph relation is not representative of the actual situation in the pigeon and the cat.

relatively large but in the cat the perilymph constitutes only a thin rim around the membranous canal (Fig. 3 *c* and *d*). This information is easily obtained from the most precise investigation on this subject performed by Fernández & Valentinuzzi (1968). According to these measurements the diameter of the osseous horizontal canal is 0.28 mm and in this space the membranous canal has a diameter of 0.23 mm leaving a perilymphatic space of at most 0.025 mm in width surrounding the membranous canal. The perilymphatic space was even smaller in the vertical canals. If the perilymph is of the great importance ascribed to it by Anliker & v. Buskirk, the cat should have a correspondingly lower sensitivity to acceleration than either man or the pigeon. However the cat is one of the more commonly used animals for precise vestibular experiments and there has been no report that its sensitivity to acceleration is lower than in those species which have a much wider perilymphatic space. Further considering the relationship between changes in the cross-section and the radius of curvature of the membranous canals versus the body mass in different animal species as studied by Melvill Jones & Spells (1963), only the endolymphatic space seems to be relevant in this context in spite of the variations in perilymphatic space.



Fig 4 Dark-field photograph and drawing depicting the angle between the horizontal canal and ampulla in the pigeon. The bony wall of the right and left horizontal ampulla and canal is peeled off from the anterior-inferior side to show the insignificant part of the ampullary wall facing the canalicular perilymphatic space.

Comments on the Second Premise of Anliker and v Buskirk

In the schematic drawings by Anliker & v Buskirk (1971) (their figures 1 and 4) the important point which is emphasized is that the perilymphatic space ends where the ampulla presents a wall perpendicular to the assumed direction of perilymph flow The perilymphatic space does not end at a perpendicular wall however but in a space continuously tapering down to very small dimensions before meeting the ampullary wall as seen in Fig. 4

From the histological pictures presented in Figs. 5 and 6 it is also apparent that the perilymphatic connective network anchors the membranous labyrinth securely to the periosteum of the bony walls. These connections in the ampulla can always be seen in good histological sections but those around the canals are often more difficult to reproduce Therefore it is advisable to resort to dissections like those in Figs. 5 and 6 and to use dark field microscope illumination or other suitable approaches. From these dissections it is obvious that there is very little of the ampullary wall which can face the canalicular perilymph and that the membranous ampullary walls are tightly anchored to the periosteum

Comments on the Third Premise of Anliker and v Buskirk

These authors admit that vessels and thread-like structures are crossing the perilymphatic

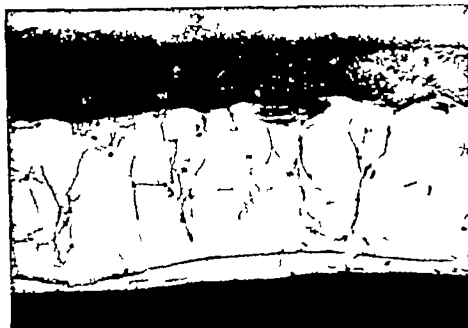


Fig. 5. Photograph of spongy network of fine connective tissue threads in perilymphatic space of the pigeon. Shown are the anterior vertical canal and part of the ampulla. The perilymphatic tissue is clearly seen. Blood vessels and an abundance of capillaries in the perilymphatic space are also present.

space but they do not believe that these connective tissue bridges could impede the assumed motions of the perilymph. This view point would be valid if such threads were found only occasionally and in small number in the canal as a whole. We believe that Figs. 5 and 6 demonstrate that the perilymphatic space is a spongy meshwork of fine connective tissue threads. In histological sections of about 20 μm thickness, this network can be adequately demonstrated. To assume that this meshwork offers no resistance to perilymph movement is to make an unreasonable conjecture.

Furthermore, if the assumption of cupula stimulation due to perilymph movements has any application, it should be valid for all species with a perilymphatic space. In cartilaginous fish and frogs (species used extensively in vestibular research) it is then expected that the sensitivity of the semicircular canals should be considerably lower for the following reasons. The walls of the ampullae are thick and cartilage-like. They strongly resist deformation and if indentated with the point of a needle, they slowly resume their shape due to the elasticity of the tissue. The whole labyrinth is suspended in a thick extremely viscous perilymphatic substance which gives the impression of being impossible to move by the accelerations due to head movements. When recording the action potential frequency of the ampullary nerve in these species it can be established that the sensitivity of the ampullae to acceleration is extremely high and that in principle no quantitative difference exists between these and other animal species.

Anliker & v. Buskirk (1971) criticized the results of earlier experiments to measure the rigidity of the ampullary wall (Dohlman, 1941). These experiments gave a rigidity value corresponding to the weight of 40–60 mg. Without presenting any new evidence they assume "that the membranous labyrinth could have been excessively pressurized" due to the removal of some of the perilymph over the ampulla in these experiments. This suggestion is contrary to simple physical principles. Admittedly the experiments (Dohlman, 1941) were made after

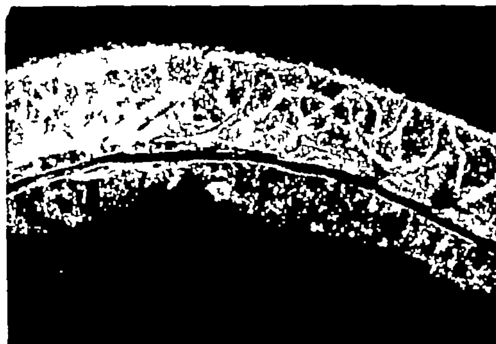


Fig 6 Photograph of spongy network of fine connective tissue threads in perilymphatic space of the pigeon. Shown are the perilymphatic tissue, blood vessels and a tight network of capillaries covering tl membranous canal wall.

removal of some perilymph covering the membranous ampullary wall. If these walls were elastic and flexible as these authors predict, removal of even a considerable part of the perilymph must necessarily result in a collapse of the unsupported membranous walls and not an increase in pressure

Consider the following simple experiment. A rubber torus (an inner tube of a bicycle tire) is filled with water and completely submerged in a water bath as shown in Fig 7 If the tube is drawn partially out of the bath and cut open at its vertex, air will be sucked into th tube, indicating that the internal pressure c the tube was less than that of the surroundin air This negative pressure is due to elasti expansion of the submerged part of the rubbe tube due to the pressure of the water cor tained in the elevated part of the tube.

In the labyrinth however the largest pres sure difference between the horizontal ampull when it is placed uppermost during the ex periment, and the lowest part of the anterio vertical canal, cannot be more than at mos

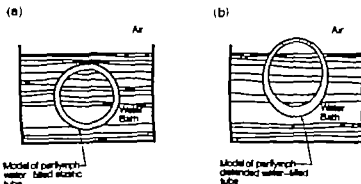


Fig 7 Model of the collapse of a wate filled torus represented by a rubber in ner tube of a bicycle tire lifted out o a water bath (see text).

3 mm of water Even if the position of ampulla and canals should be reversed, it is not easy to understand that a water pressure of 2–3 mm should be able to produce an "excessively pressurized" endolymphatic tube. Further Ewald's experiment (Ewald, 1892) involving the so-called "bridge preparation" in the pigeon, where bone and perilymph are removed from a section of the semicircular canal, always leaves an intact membranous canal. This proves that at least in this animal the walls of the canals have sufficient rigidity to withstand the pressure changes due to removal of perilymph. Further if the canal is cut, no fluid seems to escape and no air is sucked in. Therefore the statement (Dohlman 1941) that the ampulla has enough rigidity to withstand a possible impact from perilymph movement seems still to be valid.

CONCLUSION

The presence of the spongy perilymphatic tissue (Figs. 5 and 6), the angle between the canal and ampulla (Fig. 4) and the dense fibrous connections between the membranous labyrinth and the periosteum seem to be three factors which contribute to the stabilization of the membranous system and prevent any influence on cupula deflection by the perilymph. It therefore seems erroneous to consider calculations of cupula stimulation on the assumption "that the ampulla wall offers no resistance" and to disregard the influence of the perilymphatic tissue. Even if the value of the deformation resistance of the ampulla wall is inaccurate as measured by Dohlman in 1941 this resistance is not negligible and cannot be assumed to be insignificant.

In their conclusion Anliker & v Buskirk claim that they have "shown" that "it is primarily the perilymph which causes the deflection of the cupula" The premises on which these authors base their calculations, however have no factual support and are misleading as the foundation for their calculations.

A mathematical explanation for the fact that apparently the same sensitivity to physiological stimuli can be achieved in different species in spite of the great differences in perilymphatic cross-sections would have been of greater value. The discrepancy inherent in their statement "that the contribution of the perilymph to the volumetric displacement of the cupula is almost 200 times that of the endolymph" when calculated in terms of human dimensions is apparent upon consideration of the facts that the canals of the cat have a cross-sectional perilymph area only one third that of the endolymph and that there is no evidence that the sensitivity to stimulation is different in these two species.

ZUSAMMENFASSUNG

Die Behauptung von Anliker & v Buskirk (*Acta Otolaryng* (Stockh.) *72* 93), dass die Perilymphe einen kleineren Widerstand gegen Flüssigkeitsbewegungen darbieten sollte als die Endolymphe wegen einer Differenz in der Querschnitts-Area dieser beiden Flüssigkeits-Rohre, wird zurückgewiesen. Das Netzwerk von bindegewebigen Fäden und Blutgefässen die den Perilymph-Raum durchsetzt, sowie die halbmondförmige, und nicht zirkelrunde Querschnitts-Area dieses Raumes, bietet einen beträchtlichen Widerstand der von Anliker et al. für ihre mathematische Behandlung vernachlässigt wurde. Sie haben auch eine resistenzlose perpendikulare Wand der Ampulle angenommen, was morphologisch und physikalisch nicht mit bekannten Erfahrungen übereinstimmt. Es wird an diesen Punkten nachgewiesen, dass die Grundlagen für die Berechnungen von Anliker et al. sich auf fehlerhafte Annahmen stützt und dass nichts vorgebracht worden ist was die allgemein umfasste Ansicht von der Funktionsweise der Endolymphe für die Sinnesepithel-Reizung ändert.

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DOES PERILYMPH MODIFY CUPULA DEFLECTION?

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Abstract The concept of perilymphatic actuation of the cupula proposed by Anliker & VanBuskirk (Acta Otolaryng 72, 93–100, 1971) has been reviewed and found that their model is based on a quite erroneous concept of the anatomy of the temporal bone. Careful study of serial slides of the temporal bone shows that the cupular deflection is caused primarily by flow of endolymph, and therefore, the mathematical model based upon a faulty view of the anatomy of the system cannot be accepted.

Since the first observation of the vestibular end-organ of pigeons and rabbits by Flourens (1824) at the beginning of the nineteenth century the vestibular apparatus has been studied morphologically in great detail, and modern anatomical and physiological investigations have added more information describing the labyrinth. It has been well accepted that cupular deflection is due to flow of endolymph and a few mathematical models have been developed for the cupula–endolymph system based upon the endolymphatic actuation of the cupula.

Recently Anliker & VanBuskirk (1971) suggested that the deflection of the cupula is caused by primarily the perilymph and they developed a new model of the perilymph–endolymph–cupula system. The concept of perilymphatic actuation of the cupula proposed by Anliker & VanBuskirk (1971) cannot go unchallenged However sound mathematically it is unfortunately based on a quite erroneous concept of the anatomy of the vestibular end-organ. Anliker & VanBuskirk's Fig 1 which depicts an artist's drawing of their idea of the anatomy of the ampulla simply does not exist in reality It shows the dome of the membranous ampulla tightly up against the bony ampullary wall, suggesting that there is no perilymphatic cistern between the membranous and bony ampullary walls, and it is, therefore, impossible for perilymph to get past the membranous ampulla.

However even a superficial perusal of temporal bone sections demonstrates in both the human (Fig. 1) and the animal (Fig. 2) a substantial supra-ampullar cistern, allowing for as easy flow of perilymph past the ampulla as around the semicircular duct. Furthermore, the fibrous tissue strands supporting both the membranous semicircular duct and the dome of the ampulla could be expected both to impede perilymph flow as well as prevent deformation of the membranous ampullary wall.

In checking with Igarashi (1972) Anliker & VanBuskirk's source (Igarashi, 1969) of there being "no evidence of perilymphatic cisterns above the membranous ampulla" it is apparent that Igarashi's letter to VanBuskirk was misinterpreted.

Based on available information on the semicircular canals, cupular deflection is not caused by flow of perilymph but caused by flow of endolymph One day we must learn how the vestibular system works and learn dynamics of the semicircular canals so that we can determine if the various mathematical models of it are sound. Meanwhile any "new model" based upon a faulty view of the anatomy or physiology of the system cannot be accepted



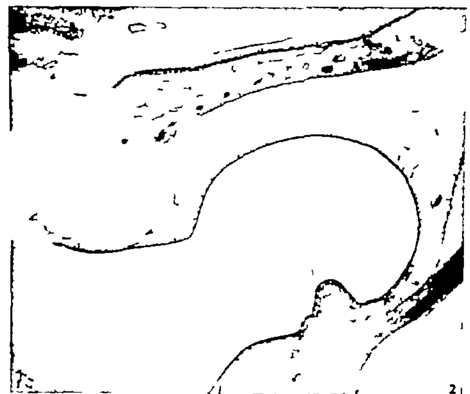


Fig 1 Human temporal bone H & E stain right center ampulla, left center utricle The supra-ampullar and peri-ampullar cisterns are evident and rather capacious.

Fig 2 Temporal bone section of the chinchilla, H & E stain. The supra-ampullar cistern is evident In this animal, artifact is less than in the human, due to perfusion, and the network of connective tissue strands between the membranous and bony ampullary walls are more clearly evident. The anatomic implication of this network is clear It would be expected not only to impede perilymph flow but work against distortion of the membranous ampullary wall.

ZUSAMMENFASSUNG

Die Vorstellung, dass die Cupula durch die Perilymphe in Bewegung gesetzt wird, wie es von Anliker und VanBuskirk vorgeschlagen worden ist, ist einer näheren Prüfung unterzogen worden. Es ergab sich, dass ihr Modell auf einer gänzlich irrigen Auffassung von der Anatomie des Schläfenbeins basiert. Eine sorgfältige Untersuchung von Serienschnitten des Schläfenbeins zeigt, dass die Bewegung der Cupula primär durch den Fluss der Endolymphe bewirkt wird. Das mathematische Modell, das von einer fehlerhaften Auffassung von der Anatomie des Systems ausgeht, kann somit nicht akzeptiert werden.

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NYSTAGMUS INHIBITION AS AN EFFECT OF EYE-CLOSURE

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Abstract In the present investigation the nystagmus response during rotation with open eyes in darkness was compared with the response recorded during eye-closure. Eye-closure reduced the induced nystagmus response and in 20 out of 30 subjects the response decreased to such an extent that it was impossible to record by electronystagmography A relation was found between vertical eyeball deviation during eye-closure and the degree of nystagmus inhibition. From the present investigation it appears that examinations of the peripheral vestibular function carried out while the subjects' eyes are closed often give mislead ing recordings which may result in incorrect conclusions. The best way of recording vestibular induced nystagmus, therefore is to test the subjects with eyes open in total darkness.

It is well known that identical vestibular stimuli may cause different nystagmus re sponses in different individuals, but also in the same individual on different occasions. A rge number of investigations deal with the ssible reasons for such variations. Some of these causes are fairly well known such as the effect of habituation (Aschan, 1954 Dodge 1923 Forsman et al. 1963 Griffith 1920 Groen, 1957 Hamersma, 1967 Hallpike & Hood, 1953 Henriksson et al., 1960 1961 Hood & Pfaltz, 1954 Lidvall, 1961 McCabe, 1960 Sokolowski, 1963), of smoking (Tibbling, 1969 Tibbling & Henriksson, 1968), of visual fixation (Aschan, 1955 Aschan et al., 1956 Collins et al. 1961 Hallpike & Hood, 1953 Hamersma, 1967 Henriksson 1956 Mahoney et al. 1957 Sokolowski 1963 1966 Stahle 1958) similarly the effect of variation in mental alertness (Barber & Wright, 1967 Collins, 1962; Collins & Guedry 1962, Collins et al. 1961 1962 Gillingham, 1969 Lidvall, 1961 Mahoney et al. 1957 McLay 1962, Sokolowski, 1963, 1966).

Nystagmus inhibition is differently defined by different authors and the phenomenon is referred to in different experimental and clinical conditions. Most frequently it means that no nystagmus or only a feeble response is obtained in spite of a vestibular stimulus known to be capable of eliciting a certain response (Barber & Wright 1967 Gillingham, 1969 Groen, 1957).

The inhibition may be of a transient peripheral origin, a kind of adaptation to a repeated stimulus. It may also be of an active" central origin, suppression considered one of the brain s methods of damping or regulating repetitive or unwanted stimuli (McCabe et al., 1964). The mechanism of this "active" suppression is still unknown however It might be caused by activity reaching the end-organ through the efferent pathways within the vestibular nerve (Dohlman et al. 1958 Gleisner & Henriksson, 1964 Sala, 1965 Silverstein, 1962) reducing the peripherally elicited afferent activity at the level of the haircells, and in this way suppressing the manifestation of the peripheral vestibular stimulation. Groen (1957) is of the opinion that the inhibition takes place in the synapses of the neurons of the central vestibular system and owing to this mechanism the peripherally released impulses will not reach the oculo-motor nuclei.

There are obviously still other inhibiting

mechanisms to consider A kind of passive" inhibition is observed during sleep and hypnosis (Aschan et al. 1962, Johner & Perlman, 1968) and according to Barber & Wright (1967) the same phenomenon occurs in subjects who are unusually sleepy

There is no doubt that the status of mental alertness in the subject is an important factor when the vestibular function is tested. Many authors therefore recommend some kind of mental activity during the tests to avoid nystagmus inhibition.

For the same reason visual impressions are excluded during examinations of the vestibular function to avoid inhibition by visual fixation. This exclusion is made either by eye closure or by examining the subjects in total darkness.

Using a photo-electric technique which made the subjects keep their eyes open in darkness during the test, Johnson & Torok (1970) found that the habituation effect of repeated rotatory stimulations did not take place. Torok (1970) has also shown that there is no difference in response between tests carried out during forced alertness—with mental activity—and tests made when the subject's attention is relaxed— just trying to feel comfortable and keeping the eyes open in darkness" These two investigations show that a forced state of alertness is no prerequisite for an adequate response when the examinations are carried out with open eyes in darkness. Enough mental energy seems to be provided when the subject concentrates on keeping his eyes open. The position of the eyeballs during eye-closure has been studied by many authors. About 150 years ago Bell studied the position of the eyeballs behind closed eyelids. He found that the eyeballs were elevated during eye-closure and stated that this was a physiological position of rest" not only during sleep but also in conscious subjects with closed eyes in darkness.

Using a cinematographic recording of the behaviour of the eyeballs during and after eye closure, Hall (1936) discovered that the eyeballs always assumed the same position of rest in the same subject but that this position might differ from one subject to another He found that most often in about 88% the eyeballs turned upwards and remained elevated until the eyelids opened. In some cases the eyeballs did not move at all, and in others they moved downwards. In all of the cases Fluur & Eriksson (1961) found an initial elevation of the eyeballs at eye-closure which, however was followed by a downward movement after a few seconds.

Perhaps this change of position of the eyeballs during eye-closure may affect the vestibular nystagmus. Aschan et al. (1956) however found similar responses to similar optokinetic stimuli when making recordings with the eyeballs in two different vertical positions, and concluded from this that Bell's phenomenon does not explain the differences between recordings made with the subject's eyes open or closed.

The aim of the present investigation was to find out if vestibular nystagmus elicited by angular stimulation was changed by eye-closure even though visual fixation had already been eliminated by total darkness

METHOD

Both labyrinths were given vestibular stimulation by clockwise angular acceleration of 62 /sec² for 1 8 sec, followed by a constant velocity of 120 sec. The subject was seated in the rotation chair in total darkness with his head fixed and bent forward 30 so as to place the lateral semicircular canals in the plane of rotation. The recordings were made in the horizontal plane of both eyes together and in the vertical plane of the left eye alone. By using a d.c.-technique with an infinite time constant it was possible to record the position of the eyeballs also. The recordings were made on a four-channel writer (Mingograf 81 Elema-Schönander Sweden) and specially devised d.c.-electrodes (Elema-Schönander Sweden) were used.

MATERIAL

The material consisted of 30 healthy people, aged 18–24 years, mostly students, 8 of whom were females and 22 males, with no history of labyrinthine disorders and no previous experience of vestibular experiments.

Performance of the test

Prior to each test the horizontal and vertical eye movements were calibrated for 20 All tests were carried out in total darkness. Each subject was exposed to 2 different tests of 1 minute clockwise rotation with an intervening pause of 5 minutes.

1 Open eyes. the subjects were required to keep their eyes open and as far as possible to avoid blinking during the whole test.

2. Closed eyes the subjects were told to close their eyes lightly throughout the experiment and this eye-closure was initiated 3–6 seconds before the start of the rotation. Every second test-subject was exposed to the same test but in the opposite order

Analysis of the recordings

The per rotatory nystagmus was measured and analysed by counting the frequency and by adding up the distances in millimetres from the peak of each nystagmus beat to the base line of that beat. These values were converted to eye movement degrees by means of the calibration data. Each quality was calculated in 4 periods, each of 5 sec, comprising the first 20 sec of rotation. The vertical deviation of the left eyeball during eye closure was also recorded and studied.

RESULT

Nystagmus inhibition during eye-closure

Regular and rhythmic per rotatory nystagmus was observed in all 30 subjects when recordings were made with open eyes in darkness

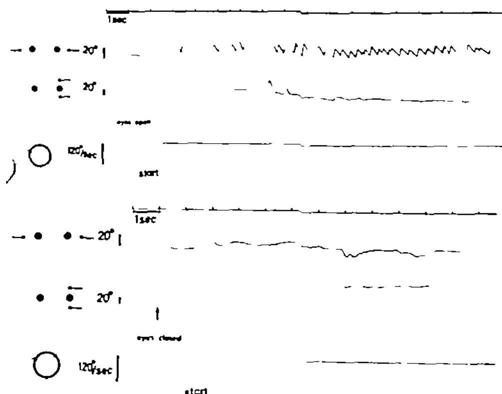


Fig 1 Reproduction of a normal nystagmus response during rotation with open eyes in darkness (above), and in the same subject a complete inhibition of nystagmus with eyes closed during the rotation (below).

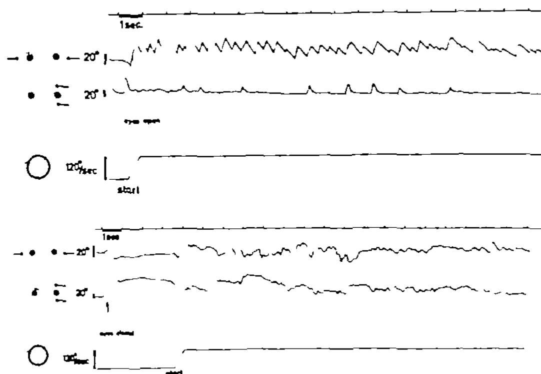


Fig. 2. Reproduction of a normal nystagmus response during rotation with open eyes in darkness (above), and in the same subject a reduced and distorted response with eyes closed during rotation (below).

During eye-closure no nystagmus or a very reduced and distorted response was observed in 20 out of 30 subjects. The reduction and distortion in these 20 cases were so pronounced that these recordings were scored and plotted as zero. A partial reduction of the per-rotatory nystagmus was observed in 9 out of the other 10 subjects while in 1 subject there was a nystagmus response of somewhat higher intensity.

Figs. 1–3 present original d.c.-recordings of horizontal and vertical eye-movements and eye-positions before and after start of rotation with open and closed eyes in darkness, together with a recording of the angular velocity of the rotating device. As appears from the figures, regular and rhythmic responses occur during rotation with open eyes, while during eye-closure different degrees of nystagmus inhibition within different subjects can be observed.

In all subjects, diagram A in Fig. 4 shows the mean of the total eyeball deviation in the slow component during the first 20 sec of rotation. The mean changed from 533 /20 sec with open eyes to 101 /10 sec during eye closure. The 20 subjects with no nystagmus during eye-closure are excluded from diagram B. In spite of this exclusion a difference in the nystagmus response between rotation with open eyes and rotation during eye-closure could be observed in the resting subjects. Diagram A in Fig. 5 presents the mean frequency of beats during the first 20 sec of rotation in all subjects. The mean with open eyes was 2.5 beats/sec and during eye-closure 0.6 beats/sec. The 20 subjects with no nystagmus during eye-closure were excluded from diagram B and there was also a difference between open and closed eyes. Figs. 6 and 7 show the distribution of these calculated qualities when counted during 5-second periods. In these two figures only the 10 subjects with nystagmus during eye-closure are plotted.

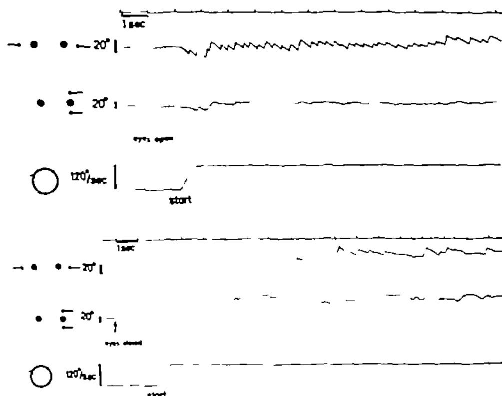


Fig. 3. Reproduction of a normal nystagmus response during rotation with open eyes in darkness (above), and in the same subject a partial inhibition of the nystagmus response when the eyes are closed during rotation (below).

Position of eyeballs during eye-closure

In all subjects there was an initial elevation of the eyeballs at eye-closure. From this initial elevation the eyeballs turned down again behind the eyelids in some of the cases, while in others the eyeballs remained elevated as long as the subjects were told to keep their eyes closed. The speed and degree of the downward movement varied from one subject to another. Repeated tests showed the same patterns in the same subjects though the patterns could be slightly or moderately modified. Fig. 8 shows examples of different patterns of eye-balls positions during eye-closure.

Relation between vertical eyeball deviation during eye-closure and nystagmus inhibition

In the recordings with total nystagmus inhibition during eyeclosure the eyeballs remained elevated behind the eyelids as long as the subjects were told to keep the eyes closed (Fig. 1). From the recordings with partial inhibition of nystagmus during eye-closure it appeared that the eyeballs turned down behind the eyelids after the initial elevation (Fig. 3). Fig. 9 shows that different positions of the eyeballs during eye-closure are combined with different degrees of nystagmus inhibition. In Fig. 9*a* the eyeballs remain elevated during eye-closure and the induced nystagmus is completely inhibited during this period. The nystagmus is not released until the subject is told to open his eyes, at which moment the eyeballs turn down again. Fig. 9*b* shows an initial brief eyeball movement upwards at eye-closure and a simultaneous nystagmus inhibition during this very period. The eyeballs then turn down behind the eyelids and the nystagmus is released again though the eyelids are still closed.

A statistical evaluation has been performed using Student's *t*-test. The mean frequency

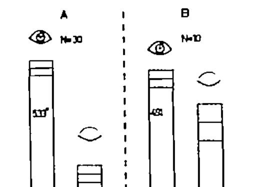


Fig 4 Total of eye-deviation in slow components during first 20 seconds of rotation with open and closed eyes in darkness. Results are given as mean ±S.E.M ( ). Diagram A gives the results with all 30 subjects included. Diagram B gives the results when the 20 subjects with no nystagmus during eye-closure are excluded.

during the first 20 seconds of rotation was significantly higher with open eyes than with closed eyes ($p<0.001$***). The mean total eye-deviation in the slow components was also significantly higher with open eyes than during eye-closure ($p<0.005$**). The statistical evaluation was performed with the mean of all subjects examined with open eyes and the mean of the 10 subjects with nystagmus during eye-closure

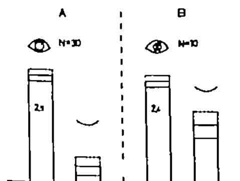


Fig 5 Frequency of nystagmus beats during rotation with open and closed eyes in darkness, counted during first 20 sec of rotation. Results are given as mean ±S.E.M Diagram A gives the results with all 30 subjects included Diagram B gives the results when the 20 subjects with no nystagmus during eye-closure are excluded.

DISCUSSION

Nystagmus inhibition as an effect of eye-closure

As this study has shown eye-closure may reduce induced nystagmus response and sometimes even inhibit the response completely On the other hand, many authors have found that eye-closure facilitates the induced nystagmus response and prolongs duration of nystagmus (Aschan et al., 1956 Hamersma, 1967 Sokolowski, 1963 Stahle, 1958). Though these different results seem irreconcilable there is no real contradiction. In the first case, the nystagmus response obtained with open eyes is compared with the response obtained during eye-closure, and both tests are carried out in darkness. In the second case the comparison is between open and closed eyes in light and the difference found in these tests must be ascribed to visual fixation. As visual fixation in the present study is already eliminated with darkness, there is no comparison between visual fixation and "non-visual-fixation" but between open and closed eyes.

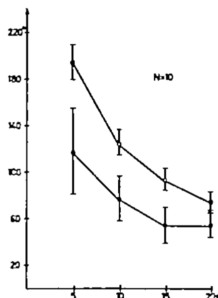


Fig 6 Total of eye-deviation in slow components with open (○), and closed (●) eyes in darkness counted during 5 sec periods from start of rotation Results are given as mean ±S.E.M. Only the 10 subjects with nystagmus during eye-closure are plotted.

ing eye-closure and nystagmus inhibition. A more pronounced inhibition occurred when the eyeballs remained elevated during eye-closure than in cases where the eyeballs turned down again after the initial elevation. It was also seen how the nystagmus beats returned or started when the eyeballs turned down from the elevated position. In this case it was necessary to test the possibility that the change in the electrical field projection was responsible for the change of the recorded nystagmus response. This was checked by calibration experiments with the head bent forwards 30° and backwards 40° while the subject was made to make the same calibration movements with his eyes. Bending of the head in this way still allowed fixation of the calibration target. In this way the subject's eyes made the same horizontal deviation though with the eyeballs in a different vertical position. All of these calibrations, however, gave the same deflection of the tracing. From this it can be concluded that the changes in the electrical field projection is not responsible for the change of the recorded nystagmus response.

Changes in the activity (inhibition or activation) of the different extra-ocular muscles at eye-closure due to the reciprocal innervation may be in conflict with the vestibularly induced activity and thus cause nystagmus inhibition.

It is observed how the tonic activity of the extra-ocular muscles is inhibited during sleep (Björk & Kugelberg, 1953; Breinin & Moldaver, 1955), and it is also known that vestibular stimulation during sleep causes no nystagmus response. As the proprioceptive system of the body also includes the extra-ocular muscles (Breinin, 1957), it might be assumed that a stimulation of the muscles turning the eyeballs upwards might cause a change of tonus in the other extra-ocular muscles. This might also be in conflict with the vestibularly induced eye movements. The reciprocal innervation causing the elevation of the eyeballs at eye-closure also changes the mechanical prerequisites for the eyeballs' movements in the horizontal plane. When the eyeballs are elevated the relation between the insertion of the eye-muscles and the axis of rotation is changed and perhaps this might be one of the factors contributing to the variations.

CONCLUSION

This investigation shows that recording of induced nystagmus during eye-closure often gives reduced and distorted responses which might lead to incorrect conclusions about the peripheral vestibular function. It is well known that there is a considerable variation of the nystagmus output owing to different experimental conditions. The present investigation has shown that these variations are more pronounced when the tests are made with the eyes of the subject closed. As the eye muscles seem to have no position of rest (Björk, 1954; Breinin & Moldaver, 1955), it seems to be in accordance with physiological conditions to investigate vestibular induced eye-movements with the eyes open in darkness when only the vestibular induced activity affects the movements of the eyeballs. This is preferable to examining the subjects during eye-closure when both the activities evoked by the reciprocal innervation and the proprioceptive system might be in conflict with the vestibular induced activity. It may seem impractical to record nystagmus in total darkness, but in our laboratory the technical equipments are arranged so as to make it possible to work from outside the dark room. This arrangement seems to be well worth the trouble and the expense.

ZUSAMMENFASSUNG

Durch Winkelstimulation ausgelöster Nystagmus wurde an 30 gesunden Versuchspersonen studiert. Die durch Drehbewegungen ausgelöste Nystagmusreaktion wurde an Personen mit geöffneten Augen mit derjenigen bei geschlossenen Augen verglichen. Sämtliche Versuche wurden in vollkommener Dunkelheit durchgeführt. Bei Lidschluss verringerte sich der induzierte Nystagmus, so dass bei 20 von 30 Versuchs-

personen keine Reaktion mehr elektromyografisch festgestellt werden konnte. Möglicherweise besteht ein Zusammenhang zwischen einer Aufwärtsbewegung des Auges bei Lidschluss und dem Ausmass der Nystagmusverringerung. Schlussfolgerung, dass eine Fehlerquelle bei der elektronystagmografischen Aufzeichnung von durch Drehbeschleunigung ausgelöstem Nystagmus behoben werden kann, wenn die untersuchte Person während des Versuches in vollkommener Dunkelheit die Augen offen hält anstatt sie zu schliessen. Aus der vorliegenden Untersuchung geht hervor dass ENG-Aufzeichnungen mit geschlossenen Augen oft zu irreführenden Resultaten führen, die falsche Rückschlüsse betreffs der peripheren vestibulären Funktion zur Folge haben können.

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CENTRAL MASKING IN NORMAL LISTENERS

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Abstract. The central masking phenomenon (CM) was studied with a clinical audiometric paradigm in a group of 40 normal-hearing subjects Contralateral maskers of wide-band noise and narrow-band noise were used each at 40 dB SL to evaluate thresholds for 500, 1 000, 2 000 and 4 000 Hz tones. CM was shown to increase in dB with increase in frequency of the test tone and with decrease in masker bandwidth. A corrective factor of 5 dB to 10 dB was suggested to account for the effect in clinical audiometric evaluation.

Central masking (CM) is a recognized phenomenon demonstrated by a shift of auditory threshold in one ear upon presentation of a contralateral masker That is, increased intensity is necessary to maintain threshold in the test ear when a contralateral masker is at a level which is not intense enough to directly shift the threshold of the test ear by transcranial stimulation. Various investigators have demonstrated that the true CM effect is not due to transcranial physical stimulation of the test ear nor to activation of the bilateral acoustic reflex. Therefore, due to lack of evidence regarding these strictly peripherally based phenomena, it has been hypothesized that the effect is somehow mediated by central auditory pathways with or without possible efferent fiber participation (Ingham, 1957 and 1959 Lidén et al., 1959).

Wegel & Lane (1924) provided the first modern description of the phenomenon and called it central masking" Ingham's more recent work provided the basis for contemporary investigations of CM under the paradigm of psychoacoustic experimentation. Zwislocki and his associates (1965 1966, 1968) and Dirks and his associates (1964 1965 1966) have extended the knowledge of CM in two series of experiments evaluating various parameters including frequency intensity and temporal aspects of stimulus versus masker designs. Their work was with pulsed and continuous stimuli and maskers under conditions not usually encountered in traditional clinical pure tone threshold evaluation. Their findings suggested that the CM effect (in dB) increases with increased intensity of the masker that it has its maximum effect upon initial introduction of the masker with quick reduction to a relatively stable shift after about 200 msec onset, that the shift decreases as the spectrum level of the masker is broadened around the test tone and that it is statistically stable and repeatable

The use of masking in one ear is necessary in the clinical evaluation of threshold whenever some critical difference is shown between the two ears so as to prevent a "shadow" response from the better ear A conventional point of view suggests the need for masking in the better ear for air-conduction thresholds whenever the bone-conduction threshold for that ear is about 50 dB better than the air conduction threshold for the poorer (test) ear The need for contralateral masking more often is required in bone-conduction measurements

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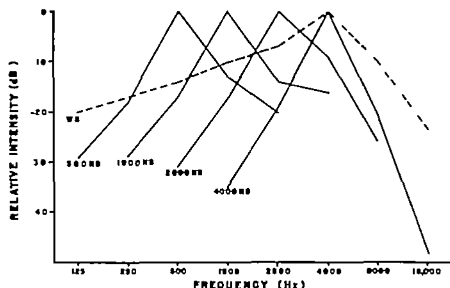


Fig 1 Acoustic spectra of wide-band (WB) and four narrow-bands (NB) of white noise. Each curve represents the noise at an overall 80 dB SPL. Identical relative curves (within _ dB) were produced at 60 dB overall SPL.

where interaural attenuation may be as low as 0 dB

The investigation of CM as a phenomenon in the clinical evaluation of hearing has received minimal scientific attention. A number of authors have suggested a general figure for the threshold shift. Palva (1954) characterizes the change in threshold as "generally less than 10 dB" Lidén et al. (1959) state that the effect is 5 to 15 dB remaining relatively constant as the masker level increases. An approximate 5 dB CM figure also has been suggested by Studebaker (1964) Price (1971) and artin (1972) These reports were in terms f general clinical observations without formal investigation

The experiment reported here was completed to determine the CM effects in normal listeners under the paradigm of clinical audiometric techniques, stimuli and maskers. Effects of test frequency and masker spectrum were evaluated statistically as an initial step toward adequate description of the phenomenon as a guide for the clinician

EXPERIMENTAL DESIGN

Frequencies chosen for evaluation were 500 1 000 2 000 and 4 000 Hz These represented a range appropriate for clinical as well as experimental, use without introducing problems of tactual stimulation (from lower frequencies) or problems of measurement reliability and validity (from higher frequencies).

Experimental conditions included measurement without contralateral masking and with wide-band (WB) white noise and narrow-band (NB) white noise contralateral maskers. These types of maskers are both in general clinical use.

A 40 dB sensation level (SL) contralateral masker was used. This level is often required to mask out a normal contralateral ear in clinical audiometry Further although this level might produce CM (as desired in this study) it was not great enough to mask the tone in the contralateral (test) ear by transcranial stimulation (Saunders & Rintelman, 1964 Dirks & Malmquist, 1965 Dirks & Norris, 1966 Studebaker 1967 Shimizu 1969).

The design provided different entry points to a consistent serial order of presentation for four frequencies by three conditions. A different entry point was drawn blindly for groups of three to four subjects. This method was used to help preclude learning practice and some order effects.

METHOD

Subjects

Forty normal-hearing adults served as subjects for the experiment. All subjects had normal hearing bilaterally (defined as −5 dB hearing level (HL) through 15 dB HL, ISO 1964) at octave intervals for the frequency range 250 Hz through 8 000 Hz. They were between the ages of 19 and 39 with a mean age of 27 1 years. All subjects were unpaid volunteers who were experienced in taking hearing tests.

No subject was used who had a −10 dB HL due to the fact that this was the limit of the audiometer and even better hearing was possible. An additional criterion was that no subject showed greater than a 10 dB difference between threshold for the two ears at any frequency This choice was made partly due to requirements for a subsequent experiment which was performed but is not reported here

Test environment and equipment

Testing was completed in an Industrial Acoustics test suite, Model 1600 ACT The basic equipment used for the study was an Allison Model 22 audiometer The signals were pre sented through TDH 39 earphones mounted in MX/AR cushions. The calibration and linearity of the audiometer was checked and monitored appropriately with a Brüel and Kjaer sound level meter

The audiometer served as the source for the pure-tone stimuli and the WB noise masker The NB masking signal was supplied by the Allison Model 26 NB masking filter attachment for the Model 22 audiometer Octave band spectral analysis of the two types of white noise were determined with the Brüel and Kjaer equipment. The acoustic spectra are shown in Fig 1

Determination of threshold sensitivity

Air-conduction threshold measurements were made in the following frequency order 1 000 2 000, 4 000, 8 000 recheck of 1 000 500, and 250 Hz. Intensity levels were varied in steps of 5 dB Presentation of the tone was for a duration of about one to two seconds. The tone was first presented at 40 dB HL. When the subject signal indicated that the tone was heard, the examiner then attenuated it to a −10 dB HL and ascended in 5 dB steps until the subject again signaled that the tone was heard. The latter procedure was repeated until the lowest intensity level was established at which the subject heard the tone two out of four presentations. This point was designated as threshold.

Threshold measurements for the masking signals were made immediately following the establishment of the pure-tone thresholds. If the two ears were exactly the same for the pure-tone measurements, the right ear arbitrarily was selected for the tone stimulus and the masker thresholds were made only for the left ear In cases where there was a 10 dB or less difference between ears, the speech frequencies were averaged and the better ear was used for the masker presentation. This precaution was made to reduce the possibility of the masker affecting the peripheral mechanism of the test ear by cross-hearing.

Masker threshold measurements were made in the following order WB white noise and then NB white noise for 1 000 2 000, 4 000 and 500 Hz bands. Sensitivity evaluation was made in 5 dB steps using the ascending technique and the 50% criterion as previously described.

Evaluation of CM

Prior to the evaluation of threshold for each frequency and each time it was tested, the subject heard a reference tone of that fre quency at about 20 dB SL. Subjects were in structed to disregard the noise when the threshold was established in the presence of the contralateral maskers. The following order was used during the experimental procedure (1) the subject was presented with the reference tone for the frequency (2) the reference tone was terminated, (3) the masker ed on and about two seconds la

Table I *Amount of central masking (in dB) produced under two experimental conditions*

Wide-band (WB) and narrow-band (NB) maskers are shown according to sensation level

	Contra-lateral masking	Test frequency (in Hz)			
		500	1 000	2 000	4 000
Mean	40 dB WB	1.8	2.8	3.0	4 6
	40 dB NB	3.5	3.5	4.3	6.6
S.D	40 dB WB	2.7	3.2	3.2	3.5
	40 dB NB	3._	2.8	3.3	3.2
Range	40 dB WB	0–10	0–10	0–10	0–10
	40 dB NB	0–10	0–10	0–10	0–15

was presented at the previously determined unmasked threshold for about one or two seconds. If there were no response the tone and masker were terminated a 20 second rest period followed and the procedure was repeated with the tone presentation at the next higher 5 dB SL. Each NB masker was used only in the evaluation of its comparable single test frequency CM was determined by comparing the unmasked and masked thresholds.

RESULT

Date from which results are drawn are present in Table I

Frequency effects

Two significant results merit attention. First, appreciable amounts of CM were shown for all frequencies under at least one experimental condition in terms of mean CM Second, 10 dB or greater CM was shown for all frequencies under all conditions by one or more subjects that is, in terms of individual test results.

Individual Wilcoxon tests (Siegel 1956) were performed in order to determine if there were significant differences for all frequency comparisons under each experimental condition Table II indicates that as the difference in Hz between test frequencies became greater the obtained CM difference for those frequencies tended to become significant. This tendency

Table II *Difference scores (Wilcoxon matched-pairs signed ranks test) for central masking according to frequency of test tones for each masker*

Maskers are shown in SL for WB and NB conditions

Test frequency (in Hz)	Contralateral masker	
	40 dB WB	40 dB NB
500 vs. 1 000	1.50	0
500 vs. 2 000	2.13	0.90
500 vs. 4 000	3.30	3.65
1 000 vs. 2 000	0.44	1 18
1 000 vs. 4 000	2.16	3 49
2 000 vs. 4 000	1.93	2.82 *

Significant at 1 % level. Significant at 5 level.

was true under every condition. For example, the CM values for 500 Hz and 4 000 Hz always displayed significantly different rankings at the 0.01 level of confidence. In contrast, the CM differences between 500 Hz and 1 000 Hz were not of significance Similar results were shown for all other frequency comparisons.

Masker effects

Wilcoxon test results for masker effects are shown in Table III Results indicate that as the band width of the masker narrowed, the CM effect tended to become significantly greater

DISCUSSION

The findings of this investigation are in general accord with the results of psychoacoustic studies of CM. Occurrence of 5 dB or greater CM was greater under this clinical design than in studies previously reported.

Table III *Difference scores (Wilcoxon matched-pairs signed ranks test) for central masking according to masker conditions for each frequency*

Contralateral maskers (in dB SL)	Test frequency (in Hz)			
	500	1 000	000	4 000
40 WB vs. 40 NB	_89	1_4	_4	_44

Significant at 1 level.

Ingham (1959) and Dicks & Malmqust (1965) reported general increase in CM with increase in the test tone frequency However both studies used only pure-tone maskers or a single NB masker for all test tones evaluated. Sherrick (1961) found slight, but regular increase of CM with increased test frequency but under four sets of pulsed tone stimuli which are not comparable to the design of the present study Masker effects upon CM also generally follow results of previous psychoacoustic investigators. Results are comparable to those obtained by Ingham (1957), Studebaker (1962) Dirks and associates (1964 1965 1966) and Zwislocki et al. (1968) but each of these studies used only one type of masker and/or a single test tone under conditions not directly comparable to clinical techniques.

Clinical paradigm investigations of CM for frontal bone-conduction thresholds have been reported by Naunton (1957) and Studebaker (1962). The designs and methods of the two experiments do not allow direct comparison with this study Other rather anecdotal-type remarks of CM in clinical threshold study have been expressed by Dirks (1964), Martin et al. (1965) Price (1971), and Martin (1972) They generally advocate subtraction of about 5 dB threshold to account for CM when contralateral masking is used.

CM results from this study were separated by degree according to frequency and masker condition. Table IV shows the percentage of subjects exhibiting 0 dB 5 dB or greater CM, and 10 dB or greater CM. In seven of the eight experimental tasks performed by each subject, 50% or more of the subjects showed 5 dB or greater CM. Findings suggest that if one chooses not to subtract for CM, one may overestimate the degree of loss. In cases where masking is not necessary for air-conduction measures, but is necessary for bone-conduction thresholds, the amount of an air-bone gap shown may be underestimated.

General conclusions suggest that it is appropriate to subtract at least 5 dB to account for CM, particularly when testing at frequencies above 1 000 Hz. The use of an NB masker has gained considerable clinical support in recent years due to its increased effectiveness relative to comparable WB maskers and due to the ease with which it is accepted by the patient. These results temper the acceptance of an NM masker due to its "enhancement" of CM. A rather large proportion of the subjects showed CM of 10 dB or greater with the NB masker One may sacrifice threshold validity to some degree by using an NB masker which enhances CM by 10 dB to 15 dB

Table IV *Percentage of subjects exhibiting three categories of central masking according to SL and type of contralateral masking*

WB = wide-band. NB = narrow-band

Test frequency		Central masking (in dB) 0 (%)	5+ (%)	10+ ( )
500 Hz	40 dB WB	67.5	32.5	2.5
	40 dB NB	40	60	10
1 000 Hz	40 dB WB	50	50	7.5
	40 dB NB	35	65	5
2 000 Hz	40 dB WB	47.5	52.5	7.5
	40 dB NB	30	70	15
4 000 Hz	40 dB WB	27.5	72.5	20
	40 dB NB	5	95	30

Ingham (1957 1959) skillfully has summarized possibilities of peripheral and central origins of the phenomenon. It is obvious that the low-level masker used here could not contribute to peripheral causes of CM by cross-hearing nor through contractions of the stapedius muscle. A process involving simple distraction, factors of decreased motivation or indecisiveness under masking conditions also might be hypothesized to account for CM. In the design of this study order practice and learning effects were controlled. The highly significant frequency-related findings, therefore, would not seem to be related to mental factors which would be expected as relatively equally distributed among all frequencies.

ZUSAMMENFASSUNG

Das Phänomen zentraler Maskierung (CM) wurde an einer Gruppe von 40 Personen mit normalem Gehör mit Hilfe einer klinischen audiometrischen Methode studiert. Kontralaterale Maskierung durch hoch- und niederfrequenziges Geräusch wurde bei 40 dB SL benutzt, um die Schwelle für Töne von 500, 1 000, 2 000 und 4 000 Hz zu bestimmen. Es wurde gezeigt, dass die CM in dB zunahm, wenn der Testton an Frequenz zunahm und die Bandbreite der Maskierung abnahm. Ein Korrektionsfaktor von 5 dB bis 10 dB wurde vorgeschlagen, um den Effekt der klinisch audiometrischen Bestimmung auszugleichen.

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DIRECTIONAL AUDIOMETRY

VII. *The Influence of Azimuth on the Perception of Speech in Aided and Unaided Patients with Binaural Hearing Loss*

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Abstract Twenty patients with binaural hearing loss varying from a Pure Tone Average (PTA) of 28 dB hearing level to 45 dB hearing level were examined: The Directional Threshold of Intelligibility (DTI) was measured both without and with background noise, without and with hearing aids. Without back ground noise, the DTI with binaural hearing aids was found to be significantly better than the DTI with monaural hearing aid in 3 of the 4 positions of the signal loudspeaker With background noise, the DTI with binaural hearing aids was found to be significantly better than with monaural hearing aid in 6 of the 16 combinations of signal and noise loudspeakers. For all the 20 experimental listening conditions we found that the DTI was significantly better with binaural hearing aids than with monaural in 11 of the 20 patients. For the 16 experimental listening conditions with background noise we found a significantly better DTI with binaural hearing aids than with monaural in 13 of the 20 patients. The results indicate that binaural hearing aids are to be preferred.

As early as 1912 Soret took out a patent for headborne stereophonic hearing aids (Hirsh 1950). However although treatment by means of stereophonic hearing aids is not new there is still disagreement as to whether monaural or binaural hearing aids should be used. Many attempts have been made to throw light on this matter but the experimental conditions under which the various investigators have worked differ so that their results cannot be directly compared.

Watson (1942), Bender & Wiig (1960) Kodman (1961), Whetnall (1964), Bentze- -- -- (1965), and Jordan et al. (1967) all concluded from their experience that the advantage lay with binaural hearing aids.

Dirks & Carhart (1962) stated that binaural hearing aids seemed to be better than monaural, but they did not find the difference very pronounced. Carhart (1958) demonstrated the advantages of binaural treatment but was also aware of the difficulties involved in such treatment. Haskins & Hardy (1960) were positive about binaural hearing aids but also mentioned that patients had refused to use them. Hedgecock & Sheets (1958), Markle & Aber (1958), Wright & Carhart (1960), and Di Carlo & Brown (1960) did not perceive any dramatic difference between the effect of binaural and monaural hearing aids. However it should be mentioned that in Hedgecock & Sheets (1958) experimental condition, speech and noise came from the same loudspeaker so that their investigations would correspond more to experiments made with hearing aid with Y-cord.

Jerger & Dirks (1961) and Jerger et al. (1961) did not find binaural hearing aids better than monaural. In their experiments the head was allowed free movement with the result that the experimental subject could move the head into the most favourable position ---------- the deaf do almost as a refle

Belzile & Markle (1959) observed that in patients with conductive and with perceptive hearing loss, binaural hearing aids were better than monaural. For both groups 50% discrimination could be achieved in the presence of 10 dB more noise while wearing binaural hearing aids than could be achieved while wearing monaural hearing aid.

Since 1964 the State Hearing Center in Aarhus has used as routine to treat patients with double-sided hearing loss with binaural aids, and the clinical experience has been good. In this paper an attempt will be made to throw some light on monaural and binaural treatment with headborne apparatus by comparing the two methods of treatment.

METHOD

The apparatus and method has been described in detail earlier (Tonning 1970 1971 *a* and *b* 1972 *a b* and *c*).

Throughout the following, the dB reference level is 0 0002 dyne per square centimetre Hearing loss in dB refers to British Standard 2497 1954 The relationship between British Standard and ISO Standard is shown in Table I (See also Whittle & Delany 1966.)

The dB values of DTI (Directional Threshold of Intelligibility definition. Tonning 1971 *a*) were recorded without noise with the signal loudspeaker reproducing speech in four different positions in the horizontal plane (0 = in front, 90 = to the right 180 = behind and 270 = on the left side of the person tested).

DTI was also determined during simultaneous stimulation with white noise the signal loudspeaker was placed in each of the previously mentioned four positions in turn For each of these positions, the noise loudspeaker was placed in the same four positions, resulting in a total of 16 different combinations of positions in noise.

Statistics in this article: Wilcoxon-Test for paired comparisons, level of significance 0.05 (References: Dixon & Massey 1957 Siegel, 1956). Electronic computer was used, the programs being taken from IBM's System 360 Scientific Subroutine Package (360A-CM-03X) Version III 1968.

The DTI values of each person were first determined without the use of hearing aid. Prior to the tests with hearing aid, the volume control of the aid was adjusted to an appropriate level by means of conversation with the operator under conditions being like for all the patients tested.

MATERIAL

Twenty right-handed experimental subjects (14 women and 6 men) from 26 to 73 years old (average age 56 years, median age 60 years) were examined. Pure tone audiograms were recorded for the frequencies 125 250 500 1 000 2 000 4 000 6 000 and 8 000 Hz using a Madsen Electronics Audiometer Model OB60, calibrated according to British Standards.

The patients are listed in Table II The hearing loss is given as PTA i.e. Pure Tone Average the mean of the hearing levels at the frequencies 500 1 000 and 2 000 Hz. The greatest difference between the PTA of the two sides in any one patient was 7 dB Only 3 patients (nos. 3 6 and 18) had used hearing aids before this investigation started.

Table I *Table for transforming hearing loss in British Standard 1954 to ISO Standard 1964*

Frequency Hz	125	250	500	1 000	2 000	4 000	6 000	8 000
dB to be added to hearing loss in British Standard when transferring to ISO Standard	3.5	3.7	2.0	+ [illegible]9	0[illegible]	0 0	7.9	5.5

Table II *Patients with binaural hearing loss*

No.	PTA dxt.	PTA sin.	Type hearing loss	Sex	Age	Type hearing aid
1	45	43	Mixed	♀	57	Aditone 620
2	40	35	Sn	♀	64	Otwidan 651E4
3	38	35	Sn	♀	63	Aditone 661
4	45	40	Sn	♀	61	Oticon 565U
5	32	28	Sn	♀	57	Oticon 830U
6	37	40	Sn	♀	59	Widex 641
7	43	38	Mixed	♀	46	Aditone 620
8	40	33	Mixed	♀	47	Oticon 560S
9	37	38	Sn	♀	26	Aditone 620
10	35	37	Sn	♀	73	Aditone 661
11	40	43	Sn	♂	65	Otwidan 651E12
12	45	58	Mixed	♀	44	Aditone 620
13	38	43	Mixed	♂	60	Aditone 620
14	37	40	Sn	♀	60	Aditone 620
15	37	40	Sn	♂	28	Aditone 620
16	42	40	Sn	♀	61	Aditone 675S
17	37	40	Sn	♀	60	Aditone 620
18	40	45	Sn	♂	60	Oticon 830S
19	43	42	Sn	♂	64	Widex 641
20	40	40	Sn	♂	64	Widex 641

PTA. Pure Tone Average: Mean of the hearing levels at 500, 1 000, and 2 000 Hz.
Sn: Sensorineural hearing loss.
Mixed. Combination of conductive and sensorineural hearing loss.

All patients were first examined without hearing aids. After an adaptation period of at least 2 months with a hearing aid, the DTI was measured with hearing aid. Patients 1–10 were first examined with binaural hearing aids: after a minimum interval of a week they were examined with hearing aid on the right ear. Patients 11–20 were first examined with hearing aid on the right ear and after a minimum interval of a week with binaural aids. For the 24 hours preceding the investigations the patient had only used hearing aid on the ear/ears due to be examined with aid.

RESULT

DTI without noise both without and with hearing aids

For each position of the signal loudspeaker the mean value for DTI ($\overline{DTI}$) was calculated without hearing aid, with one hearing aid and with binaural hearing aids, and listed in Table III. It was found

1 Significantly better DTI with rightsided hearing aid compared with the DTI found without aid, for all the loudspeaker positions.

2. Significantly better DTI with binaural hearing aids compared with the DTI found without aid, for all the loudspeaker positions.

3 Significantly better DTI with binaural hearing aids than with monaural hearing aid for 3 of the 4 loudspeaker positions.

DTI in noise both without and with hearing aids

For each of the 16 combinations of signal and noise loudspeakers the arithmetic mean of the DTI values ($\overline{DTI}$) without, with monaural, and with binaural hearing aids was calculated and listed in Table IV

The test results are listed in Table V They show:

Table III *The influence of azimuth on the DTI without noise in 20 patients with binaural hearing loss, recorded without with monaural and with binaural hearing aids*

$\overline{DTI}$ The mean of DTI for each position of the signal loudspeaker

Position of signal loudspeaker	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid dxt.	$\overline{DTI}$ with binaural hearing aids	Effect of hearing aid dxt. compared with no aid	Effect of binaural hearing aids compared with no aid	Effect of binaural hearing aids compared with hearing aid dxt.
In front	46.4	34.7	31.8	Improvement	Improvement	Improvement
Right ear	44.8	32.2	30.5	Improvement	Improvement	No effect
Behind	47.6	35 7	32.2	Improvement	Improvement	Improvement
Left ear	45.1	38.2	30.0	Improvement	Improvement	Improvement

Table IV. The $\overline{DTI}$ values (= the arithmetic means of the DTI values) for the various combinations of signal and noise loudspeakers both without with monaural and with binaural hearing aids

Position of signal loudspeaker	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid dxt.	$\overline{DTI}$ with binaural hearing aids	$\overline{DTI}$ without hearing aid	$\overline{DTI}$ with hearing aid dxt.	$\overline{DTI}$ with binaural hearing aids
	Position of white noise loudspeaker: In front			Position of white noise loudspeaker: Behind		
In front	56.2	55.3	54.8	54.7	53.9	53.4
Right ear	53.7	52.5	50.4	52.2	52.0	50.8
Behind	56.4	54.6	54.5	56.3	55.8	54.8
Left ear	53.8	53.1	50.9	52.0	53.4	50.3
	Position of white noise loudspeaker: Right ear			Position of white noise loudspeaker: Left ear		
In front	54.5	53.8	51.4	53.9	52.2	51.2
Right ear	56.6	56.3	55.4	51.0	48.3	47.7
Behind	55.3	55.—	51.5	55.0	51.9	51.1
Left ear	50.9	52.9	47.6	56.0	55.8	55.1

1. Significantly better DTI with rightsided hearing aid compared with DTI without aid for 2 positions. However the DTI was found to be worse with the apparatus for 2 positions.

2. Significantly better DTI with binaural hearing aids compared with DTI without hearing aid for 13 positions.

3. For 6 positions significantly better DTI was found with binaural hearing aids than with monaural hearing aid.

With a monaural hearing aid the listening position appears to be unsatisfactory when the signal source is facing the ear without a hearing aid while simultaneously the source of noise is placed behind the head or aimed at the ear supplied with a hearing aid. Under these listening conditions significantly poorer DTI was found with monaural hearing aid than without an apparatus, whilst binaural hearing aids showed improvement of DTI.

Effect of hearing aids on individual DTI

For each patient the term DTI_{20} indicates the DTI for all the 20 experimental positions without and with background noise. DTI_{16} indicates the 16 positions with background noise.

Table V. The effect of monaural and binaural hearing aids on the DTI for the 16 various combinations

Position of signal loudspeaker	Effect of hearing aid dxt. compared with no aid				Effect of binaural hearing aids compared with re			
	Position of the white noise loudspeaker				Position of the white noise loudspeaker			
	In front	Right ear	Behind	Left ear	In front	Right ear	Behind	Left ear
In front	No	No	No	No	Improvt	Improvt	No	Im
Right ear	No	No	No	Improvt	Improvt	Improvt	No	Im
Behind	No	No	No	Improvt	Improvt	Improvt	Improvt	Im
Left ear	No	Impair	Impair	No	Improvt	Improvt	Improvt	N

It was investigated

1 The effect on DTI_{20} and DTI_{16} of hearing aid on the right ear as compared with the values found without an apparatus.

2. The effect on DTI_{20} and DTI_{16} of binaural hearing aids as compared with the values found without an apparatus.

3 The effect on DTI_{20} and DTI_{16} of binaural hearing aids as compared with a right sided apparatus.

The results are shown in Fig. 1 and indicate that under our experimental conditions binaural hearing aids are more effective.

Use of the standard diagram

In evaluating the effect of the hearing aids, the standard diagram previously described (Tonning, 1971 *a* and *b* 1972 *a* *b* and *c*) may be used. In Fig. 2 this diagram is used to illustrate how hearing aids can influence the DTI values under various experimental listening conditions for patient 16.

1 Without hearing aid, the signal loudspeaker aimed at the left ear the noise loudspeaker aimed at the right ear
DTI without noise 47 dB
DTI with noise. 49 dB.
Point plotted at A.

2. With hearing aid dxt., loudspeakers in the same positions.
DTI without noise 33 dB.
DTI with noise: 49 dB
Point plotted at B.

3 With binaural hearing aids, the same

signal and noise loudspeaker

Tect of binaural hearing aids compared with hearing aid dxt.

-ation of the white noise loudspeaker

xt	Right ear	Behind	Left ear
)	Improvt	No	No
	No	No	No
	Improvt	No	No
ovt	Improvt	Improvt	No

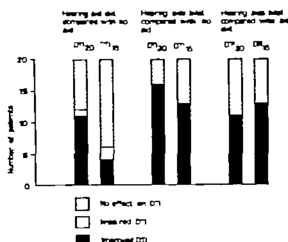


Fig 1 The effect of monaural and binaural hearing aids on the 20 patients. DTI_{20}. The DTI both without and with background noise (4 loudspeaker positions without, and 16 with background noise). DTI_{16}. The DTI with background noise (16 loudspeaker positions).

positions of the loudspeakers
DTI without noise 28 dB.
DTI with noise: 42 dB
Point plotted at C.

Point A lies farthest to the right in the diagram as an expression of the poorest DTI without noise. Point C lies farthest to the left as an expression of the best DTI without noise

All the three points lie to the right of the area of the normal hearers, expressing that DTI found under our experimental conditions without noise is poorer than for the normal hearers.

Point C lies on the isoline farthest down in the coordinate system, indicating that, in this listening situation, the patient is less disturbed by noise than in the other two situations.

The points lie on isolines which cut the normal hearers area expressing that, in the actual listening conditions in noise, our patient has DTI values which do not differ from those of the 20 normal hearers. The isoline for point C has the lowest value and point C also lies farthest to the left in the coordinate

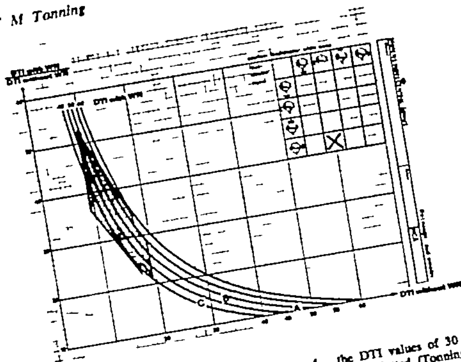


Fig. Coordinate system, illustrating the effect of monaural and binaural hearing aids under certain conditions. *Abscissa*: DTI without noise. *Ordinate*: DTI with noise divided by the corresponding DTI without noise, i.e. with the signal loudspeaker in the same position. DTI in noise is also indicated. Curved lines. Shaded figure covers the area where 95 % of the DTI values of 30 normally hearing listeners are to be plotted (Tonning, 1971 *a*). DTI values for patient 16 are plotted in the diagram. *A*. DTI without hearing aid. *B*. DTI with hearing aid on the right ear. *C*. DTI with binaural hearing aids. For further explanation see text.

system as an expression of the best DTI values both with and without background noise.

An impression of the influence both of the hearing aid and of the positions of the signal and noise sources on the comprehension of speech in the different conditions can be given by means of the diagram.

COMMENT

In no case have our calculations revealed significantly worse DTI values with binaural hearing aid treatment than with monaural. It must however be pointed out that our experimental conditions diverge considerably from listening situations in everyday life (Tonning 1971 *b*, 1972 *a*, *b* and *c*). The results therefore do not prove but suggest that binaural hearing aid treatment is advantageous.

To these measurable circumstances must be added the purely subjective remarks by some of the users of binaural hearing aids, the feeling of being able to hear with both ears. With binaural hearing aids they no longer have the impression of auditory imbalance. However the importance of such factors are hardly measurable in figures. In this connection it should be pointed out that Courtois (1972) reported good results of treating dizziness with hearing aids.

ZUSAMMENFASSUNG

Zwanzig Patienten mit binauralen Hörschäden, variierend von einem Reinton-Durchschnitt (PTA Pure Tone Average) von 28 dB Hörniveau, bis zu 45 dB Hörniveau, wurden untersucht. Die gerichtete Verständlichkeitsschwelle (DTI = Directional Threshold of Intelligibility) wurde mit und ohne Hintergrundgeräusch, mit und ohne Hörapparate gemessen.

Ohne Hintergrundgeräusch wurde die DTI mit binauralen Hörapparaten in 3 von den 4 Positionen des signalgebenden Lautsprechers signifikant besser

gefunden als die DTI mit monauralen Hörapparaten. Mit Hintergrundgeräusch wurde die DTI mit binauralen Hörapparaten in 6 der 16 Kombinationen von signal- und geräuschgebenden Lautsprechern signifikant besser gefunden als mit monauralen Hörapparaten. Bei sämtlichen 20 experimentellen Hörverhältnissen fanden wir, dass die DTI mit binauralen Hörapparaten signifikant besser war als mit monauralen Hörapparaten bei 11 von 20 Patienten. Bei den 16 experimentellen Hörverhältnissen mit Hintergrundgeräusch fanden wir mit binauralen Hörapparaten eine signifikant bessere DTI als mit monauralen Hörapparaten bei 13 von 20 Patienten.

Die Resultate indizieren, dass binaurale Hörapparate vorzuziehen sind.

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THE EFFECT OF BRADYKININ ON EUSTACHIAN TUBE AND NASAL PATENCY

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Abstract. The patency of the Eustachian tube and
nasal passages is decreased during inflammation due
to vascular congestion. The vasodilation and increased
capillary permeability due to histamine have been
known for years and treated with antihistamines.
Recent evidence of another endogenous substance
involved in inflammation, bradykinin, ten times more
active than histamine, has led to this study which
showed the effectiveness of bradykinin in reducing
the patency of the Eustachian tube and nasal passages.
A comparison was made with an even more effective
substance eledoisin, which is similar to bradykinin
but does not occur in mammals. Two drugs, aspirin
and Dilantin, that might have reduced inflammation
by blocking bradykinin, were found to be ineffective
This may shed some light on the highly variable
results obtained clinically when treating congested
nasal passages and Eustachian tubes.

Bradykinin is similar to histamine in that it
n produce an inflammatory response but is
more significant in that it is approximately
ten times more potent and has no known
blocking agent as antihistamines block hista
mine This may have clinical import in oto-
rhinolaryngology where Eustachian tube and
nasal congestion are common complaints.

There is good evidence that plasma kinins
play an active role in inflammation by provok
ing (1) vasodilation (2) increased capillary
permeability (3) accumulation and migration
of leukocytes and (4) pain (Douglas, 1970)
The effect like that of histamine is exerted
on the small venules rather than on the true
capillaries and involves separation of the junc
tions between endothelial cells (Majno et al.,
1961). Of the many vascular effects described
for bradykinin, perhaps the most acceptable
is that of venoconstriction, with selective con-
striction of A V shunts, increasing resistance
to flow through the veins, resulting in a passive
dilation of capillaries and arterioles (Sekiya
et al., 1971 Bobbin & Guth, 1968 DePasquale
& Burch, 1966) The half life of bradykinin
in blood is 0.27 minutes (McCarthy 1965).
However bradykinin upon intra-arterial injec-
tion, reaches the venous receptors in suffi-
cient quantities to induce a response. More-
over in the pathologic state as in tissue injury
or inflammation, bradykinin may be released
adjacent to or into postcapillary vasculature
and cause venoconstriction (Bobbin & Guth.
1968) Blood contains both ingredients for ki-
nin formation, kininogen and kallikrein They
are activated much as the circulating clotting
factors, by various factors disturbing the equili-
brium of the plasma. These include changes in
pH or temperature, contact with glass and
particulate matter (note Hageman factor in
kinin formation scheme Fig. 1) collagen,
microorganisms, allergic reactions and dam-
aged tissues (Douglas, 1970 Eisen & Vogt
1960).

Eledoisin an endecapeptide first isolated
from the salivary glands of two mulluscan spe-
cies, has the same effect as kinins, but is abou'
ten times more active (Nakano & Kusakari,
1966) It is similar to a "Substance P" in

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Fig 1 Factors in the formation and destruction of plasma kinins, bradykinin and kallidin (Pierce, 1968).

Fig 2 Experimental model. The greater the resistance to flow of Ringer's solution, the less patent the Eustachian tube. The greater the resistance to flow of air the less patent the nasal passages.

human plasma, as yet poorly defined. Thus, although Eledoisin is not found in mammals, it is a good sensitivity test for kinin experiments.

Anti-inflammatory drugs, such as salicylates and indomethacin, can prevent this venoconstriction of bradykinin in some isolated vascular beds, but not in others (Northover 1967 Martelli, 1967) The antihistamine tripelennamine does not affect bradykinin-evoked response, thus released histamine does not contribute to the response evoked by bradykinin Also it would appear that neither sensory nor autonomic innervation plays a role in the locally-evoked reduction in vessel diameter by bradykinin, as witnessed by data in denervated animals and phentolamine-treated animals (Bobbin & Guth, 1968).

METHOD AND MATERIAL

The techniques for measuring patency have been described before (Stovall & Jackson, 1967 Sheffield et al. 1970 Davis et al., 1970) Mongrel dogs weighing between 10 and 15 kg were the test animals. Pentobarbital was the usual anesthetic. Some of the dogs were anesthetized with alpha chloralose (Peiss & Manning, 1964), as it has been shown that pentobarbital has a depressant action on the vasomotor centers (Mizeres, 1955). Changes in Eustachian tube patency were measured by perfusing Ringer's solution through a modified Foley catheter (placed in the middle ear cavity), through the Eustachian tube, and out the nasopharynx (Fig 2). A transducer monitored the variations in pressure necessary to maintain a constant flow Perfusion rate was 1.9 ml/min.

Nasal patency was measured as a function of the resistance to humidified air infused at 2 l/min. Blood pressure was recorded from the femoral artery Drugs were injected into the cephalad end of the cannulized ipsilateral common carotid artery which was sometimes ligated proximally Drug volume was 1 cc, followed by a flush of 5 cc of Ringer's solution. Bradykinin[1] was once injected into the perfusate through the rubber tubing near the external auditory canal to demonstrate its topical action. Previous studies have shown that the patency change of the Eustachian tube to a particular drug was usually the same regardless of the route of administration (topical, intravenous, or intra-arterial) (Davis et al., 1970) The testing procedure consisted of measuring patency response to a series of increasing doses of bradykinin Comparison dose-response curves were obtained for histamine and eledoisin. Epinephrine was also used

[1] Bradykinin (Sandoz and Schwarz-Mann), Histamine as the dihydrochloride (Sigma), Eledoisin (Sandoz

several times in each experiment to test the responsiveness of the animal. In most cases, nasal and Eustachian tube patency changes were measured in the same animal.

RESULT

The dose-response curve for bradykinin is compared with that of histamine in Fig 3 A consistent feature of the drug response of the Eustachian tube is its seeming dependence on blood pressure change (Sheffield et al., 1970· Davis et al., 1970) This is also true in some cases for nasal patency (Fig. 4) Lower doses of bradykinin progressively decreased the tubal patency Doses higher than about 0 005 μg/kg resulted in reversal of the Eustachian tube patency responses. Thus, instead of leveling at a plateau at high doses, the responses often decrease in size as the dose increases producing a "peak" response. The dose at which the peak occurred was not consistent, nor was the threshold dose. Depending upon a particular animal's sensitivity these could shift ± half a log unit Most animals would develop rhinorrhea as doses increased We were able to demonstrate the extreme potency of eledoisin, as one animal responded to an intra-arterial dose of 0.25 picograms per kilogram of eledoisin

Two drugs, aspirin and Dilantin, that might reasonably have reduced the inflammatory response by blocking bradykinin were found to be ineffective, both in doses comparable to the average dose in man (1 mg/kg) as well as ten times that dose

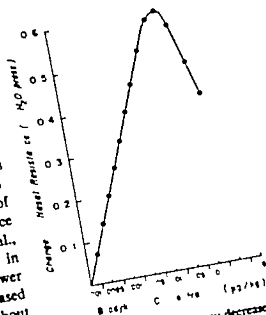


Fig 4 Nasal response. Patency decreased as resistance to air flow increased. Bradykinin was injected into the common carotid. Date is averaged from three dogs.

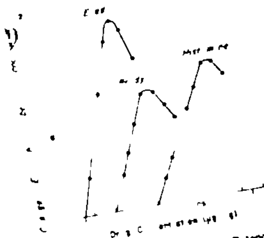


Fig 3 Eustachian tube response Patency decreased as Eustachian tube resistance increased. Drugs were injected into the common carotid. Data is averaged from seven dogs.

DISCUSSION

The Eustachian tube and nasal patency changes induced by bradykinin are probably due to the effect on the blood vessels of the Eustachian tube and nasal mucosa. As bradykinin causes vascular congestion and mucosal swelling, patency decreases. The dose response curves that were obtained are in agreement with the relative potency of the drugs as found by other workers. That is, eledoisin is approximately ten times more potent than bradykinin which in turn is about ten times more potent than histamine

It is of interest to note that a kinin-like substance has been isolated from the nasal

secretions of allergic patients who had been challenged with ragweed antigen (Dolovich et al., 1970).

ZUSAMMENFASSUNG

Im Entzündungszustand wird die Durchlässigkeit der Eustachischen Röhre und der Nasenwege durch vaskuläre Kongestion beeinträchtigt. Es ist seit langem bekannt, das Histamin Gefässerweiterung und gesteigerte Permeabilität der Kapillaren hervorruft. Antihistamin-Präparate werden bei Behandlung benutzt. Neuerdings ist eine andere endogene *Substanz, Bradykinin, die* zehnmal wirksamer ist als Histamin, bekannt geworden. Die vorliegende Arbeit beschäftigt sich mit dem Einfluss von Bradykinin auf die Durchlässigkeit *der Eustachischen Röhre und der Nasenwege*. Bradykinin wurde ausserdem mit einer ähnlichen, noch wirksameren Substanz, dem Eledoisin verglichen, das aber bei Säugetieren nicht vorkommt. Zwei weitere Medikamente (Aspirin und Dilantin), die u. U. entzündungshemmend wirken und deshalb die Wirkung von Bradykinin blockieren könnten, erwiesen sich als unwirksam. Diese Ergebnisse könnten zur Erklärung beitragen, warum man klinisch bei der Behandlung von verstopften Nasenwegen und der Eustachischen Röhre zu unterschiedlichen Ergebnissen kommt.

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LETHAL INTRACRANIAL COMPLICATION FOLLOWING AIR INSUFFLATION WITH A PNEUMATIC OTOSCOPE

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Abstract Another case is reported of lethal intracranial complication following retrograde inflation through the external meatus. The cause of death was probably emphysematous detachment of the dura over the tegmen tympani and compression of the internal carotid artery. Insufflation of the middle ear should be carried out with extreme care in cases of secretory otitis media. Hyperbar oxygenation could perhaps be of value in a case like this.

In recent years the treatment of secretory otitis media has included retrograde insufflation through the external auditory meatus to expel secretion from the middle ear and Eustachian tube using either a Politzer bag or a pneumatic otoscope (Siegle s) In 1963 Giske reported hat he had used this method for several years without any complications, and in 1968 Courtois described over 1 500 carefully carried out insufflations without complication. A modern text-book (Scott Brown et al. 1965) describes paracentesis followed by insufflation of the tympanum through the external auditory meatus as an accepted form of treatment for secretory otitis media.

However as early as 1965 Ahren & Thulin published a case with "lethal intracranial complications following insufflation in the external auditory canal in treatment of serous otitis media and due to defects in the petrous bone" Fairman et al. published a similar case in 1968 with a lethal outcome due to air embolism after retrograde insufflation of the tympanum

CASE REPORT

A 35-year-old previously healthy woman attended the out patient clinic of the Ear Nose and Throat Department, Södertälje Sweden on 10/3/69 because she has been troubled all winter by colds, and had reduced hearing in her right ear A transudate was found in the right ear which was treated by paracentesis and nose drops. Nine days later the patient returned complaining of poor hearing as before. The tympanic membrane was found to be without perforations, yellowish and sluggish with a visible fluid level. Otherwise normal ear nose and throat status. Paracentesis was carried out after surface anaesthesia with 2 tetracain. A small quantity of yellowish fluid was tapped from the paracentesis opening and retrograde insufflation through the external auditory canal was carried out using Siegle s otoscope. The insufflation was not immediately successful but change to a better suited funnel resulted in passage of air The impression obtained was, however that the air had not passed through the Eustachian tube in the normal way so insufflation was discontinued after having introduced about one bag of air.

The patient reported a bubbling sound in her right ear and a little pain in the right temporal region immediately afterwards. She lay down on a stretcher Fifteen minutes after the insufflation she felt unwell and peculiar and

complained of severe pain in the right temporal region. After another 5 minutes she became confused and restless with commencing tonic convulsions, first on the right side later generalized. There was no bleeding from the ear

An X-ray of the skull was taken as quickly as possible, but it was not possible to demonstrate intracranial air The patient was intubed by an anaesthesist, and transported to The Neurosurgery Department, Karolinska Hospital in Stockholm. About an hour after the insufflation artificial respiration was necessary and the pulse became irregular The systolic blood pressure varied between 175 and 145 mmHg. Angiography of the right internal carotid artery was carried out 3 hours after the insufflation. Markedly reduced passage of blood to the intracranial cavity was found. Only minimal amounts of contrast passed into very narrow intracranial vessels. An exploratory burr hole in the right temporal region revealed an extradural haematoma about 10 mm thick which was removed. Exploratory burr holes on the left side and in the posterior fossa showed no additional haematoma. The EEG was isoelectric and the patient was in a respirator She died 8 days later

Autopsy revealed relatively marked distention of the dura with no defects. The petrous part on the right side showed multiple punctiform reddish-brown changes very suggestive of bleeding. This was confirmed by microscopy The brain was considerably oedematous and there was total encephalomalacia. No sign of intracerebral haemorrhage There was no sign of infection. No sinus thrombosis. In the lungs there was extensive bronchopneumonia. There were no demonstrable bony defects in the petrous bone

DISCUSSION

Ahrén & Thulin (1965) investigated 94 temporal bones and found that 21% had large or small defects of the tegmen tympani. In an additional 16% there was only a thin transparent cortical bone covering the pneumatic cellulae of the tegmen tympani. In a model experiment with a Politzer bag a pressure of between 180 and 360 mmHg was recorded, which pressure was found sufficient to lift the dura off the tegmen tympani in one of two cases where there were defects in the tegmen.

Fairman et al. (1968) could not identify the pathway followed by the air from the tympanum to the carotid canal. They conclude that, as in the case of Ahrén & Thulin (1965) the air left the tympanum through one or more small hiatuses in the bony tegmen and then passed directly forwards beneath the dura to the roof of the carotid canal in the region of the foramen lacerum medium.

The cause of the symptoms in the present case was undoubtedly that air had propagated to the endocranium through pre-existent bone defects. The pathogenesis may be interpreted in different ways:

1 Separation of the dura from the petrous part thus severing blood vessels and resulting in formation of an extradural haematoma.

2. Separation of the dura and sudden compression of the cerebrum with diffuse brain damage as a consequence.

3 Air embolism as a result of air entering the venous system via ruptured thin walled vessels.

4 Compression of the internal carotid artery either by air penetrating into the bony canal of the artery or compression of the artery at the opening into the intracranial cavity by air passing between the petrosa and the dura.

The extradural haematoma shows that there has been loosening of the dura from the bone. An extradural haematoma of this size cannot however be the sole cause of the symptoms described. The volume of the bag used was 40 ml. The volume of air insufflated must therefore have been rather less than 40 ml. A sudden increase of intracranial pressure with severe compression of the brain cannot be excluded. However intracere bleedin

not demonstrated, as found by Chason et al. when studying the effect of a sudden increase in intracranial pressure in animal experiments.

Air embolism was not considered likely as the blood pressure was approximately normal and there was no cyanosis. In the present case angiography showed markedly reduced passage of blood to the intracranial cavity. It is therefore reasonable to suppose that air has left the tympanic cavity through pre-existent bony defects in the tegmen tympani, and freed the dura from the petrosa, simultaneously severing small blood vessels and resulting in the extradural haematoma described. From there the air probably forced its way further under the dura to the region of the internal carotid artery compressing it.

The only treatment that might be of any value in a case like this is probably to give hyperbaric oxygenation within few minutes (Molvær 1972). The air bubble in the tissue would decrease in volume as the pressure in the tissue increased, according to the law of Boyle–Mariotte. The volume of the air bubble would shrink also because the amount of physically dissolved nitrogen increases with the pressure. By inhalation of pure oxygen the diffusion of nitrogen from the bubble would increase. At a pressure of 3 atm there would be 6.6 ml O_2 per 100 ml artery blood which is sufficient oxygen supply for the resting organism.

Such treatment must be started before irreversible brain damage has occurred. However the possibility for such treatment is not at hand in many places.

COMMENT

In 1948 Hagness published a case with a lethal outcome as a result of air embolism after Eustachian catheterization and insufflation and he refers to four other cases in which the same treatment also resulted in death (Wanibucki, 1928. Savage, 1839. Blegvad, 1939). Hagness refers to Behrend who in 1920 had a case with lethal outcome after catheterization with insufflation on a 3 years old patient. He also mentions a number of cases in which there was loss of consciousness and transient cessation of pulse and respiration (Savage, 1839. Blegvad, 1939. Ramberg, 1940). Thornval deals with this complication in his text-book.

Áhrén & Thulin (1965) also describe a case of air embolism resulting in death after catheterization and insufflation. Both retrograde insufflation and Eustachian catheterization with inflation may obviously be dangerous procedures and should be carried out with extreme care, if indeed these methods of treatment should be used at all in patients with secretory otitis media.

ZUSAMMENFASSUNG

Darstellung des klinischen Verlaufes bei einem Fall mit letalem Ausgang nach retrograder Luftaufblasung mit Siegle Ohrtrichter im äußeren Gehörgang. Die Todesursache war wahrscheinlich eine emphysematöse Duraablösung von Tegmen tympani und Kompression der Arteria carotis interna. Luftdurchblasung des Mittelohres darf bloß mit größter Vorsicht ausgeführt werden. Überdruckbehandlung mit Sauerstoff wäre vielleicht wertvoll in diesem Falle.

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AUDIOLOGICAL ASPECTS OF ACUTE OTITIS MEDIA

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Abstract. An unselected material of 136 patients with signs and symptoms of acute otitis media were audiometrically tested with both air and bone conduction. The audiograms were made at intervals during the healing period. The first audiogram was taken before any kind of treatment. No sensorineural hearing impairments were registered. The air-bone gap averaged 20 dB initially but was closed in most cases in 20 days. No permanent hearing impairments were noted. No major differences were noted between the audiograms of patients with spontaneous rupture, myringotomy and no myringotomy

Acute otitis media is a frequent complication of upper respiratory tract infections, especially in children. It is nowadays seldom combined with serious complications as it used to be before the introduction of chemotherapeutics and antibiotics. Transient hearing impairment is, however still reported after an attack of acute otitis (Olmsted et al. 1964 Neil et al. 1966) although it is seldom permanent (Stickler et al., 1967). There are unfortunately few studies with audiometric measurements in the acute stage of the infection before any treatment and with a consequent follow-up during the restitution period.

Acute otitis media must not be considered healed until hearing is normal. Therefore, it was thought of interest to include audiological measurements while studying etiological, clinical and serological aspects on acute otitis media.

MATERIAL AND METHOD

The investigation was performed during the period September–December 1968 and comprised 237 out-patients with symptoms and signs of acute otitis media in the Otolaryngological Department, Sahlgren s Hospital, Göteborg. The age distribution is stated in Fig. 1 136 patients over 3.5 years of age were audiometrically tested with both air and bone conduction. Air and bone conduction audiometry was performed with a Camplex DA 2 audiometer calibrated according to ISO standard, 1964 The tests were made in a sound-proof room. After the otological examination bacterial and blood samples were taken for analysis (Herberts et al., 1971).

All patients were treated with either of two penicillin preparations.[1] Nose decongestants were also prescribed and the therapy was continued for 10 days. No therapeutical differences were noted between the two preparations and therefore the material was analysed as a single entity (Herberts et al., 1971).

The first audiogram was made immediately after the otitis had been diagnosed and before the patient had received any kind of treatment. Thus, the myringotomies, if any were made after the test. The second audiogram was performed after 9–11 days of penicillin treatment. The third audiogram was made after another 10 days on patients considered not healed at the first control. Some of these had continued antibiotic treatment for more than 10 days. In those cases, the drug was chosen in accordance with the sensitivity test of the organism isolated at the first visit.

The purpose of this investigation was to

[1] Penicillin-V and alpha-azido-benzyl-penicillin (azidocillin) which latter has the same antibacterial spectrum as penicillin-G but a higher effect in vitro against *H influenzae* The preparations have kindly been placed at our disposal by Astra Läkemedel AB, Södertälje, Sweden (Forsgren, U 1968).

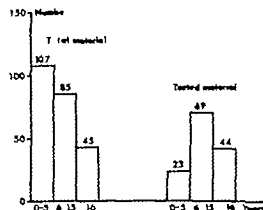


Fig 1 Age distribution.

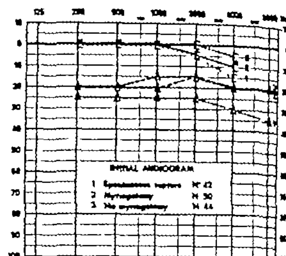


Fig 3 Mean initial audiograms for the affected ear in patients with spontaneous rupture, myringotomy and no myringotomy

study the hearing function in cases of uncomplicated otitis media. In order to elucidate the importance of spontaneous rupture and myringotomy respectively on hearing, the patients were divided in the following three groups:

1 Patients with spontaneous rupture (42).

2. Patients in whom myringotomy was performed (50)

3 Patients in whom myringotomy was not indicated (44)

RESULT

The mean hearing levels of the frequencies 250–8 000 Hz were recorded on 136 patients (Fig. 2). It can be seen that the results of the bone conduction tests (8 000 Hz not tested) did not vary at all under the infection period. The air–bone gap at the first test averaged 20 dB for all frequencies up to 4 000 Hz (Fig. 3) After 10 days of penicillin therapy the gap was considerably reduced (Fig. 4). Forty-nine patients were considered not healed at this control and were again tested after another 10 days (Fig. 3) At this occasion the air-bone gap was closed and the hearing considered to be normal in all but 6 cases with secretory otitis media.

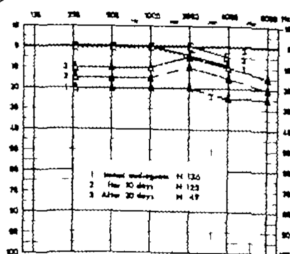


Fig Mean audiogram of the affected ear for the total patient material.

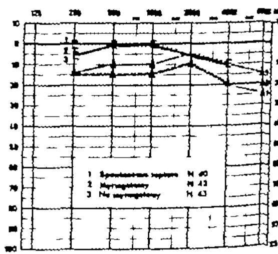


Fig 4 Mean audiograms after 10 days for the affected ear in patients with spontaneous rupture, myringotomy and no myringotomy

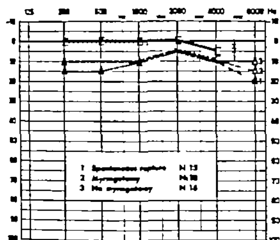


Fig. 5 Mean audiograms after 20 days for the affected ear in patients with spontaneous rupture, myringotomy and no myringotomy

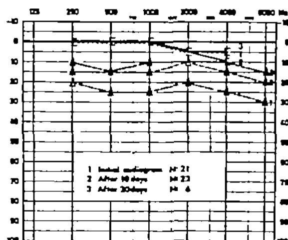


Fig. 7 Mean audiograms for the affected ear in patients with isolation of *Diplococcus pneumoniae*

The mean audiogram at different times of the three groups of patients with spontaneous ruptures, myringotomies and no myringotomy are presented in Figs. 3–5. The average bone conduction curves for the different groups were similar and without changes during the infection. There are astonishingly small differences in the hearing thresholds between the patients with spontaneous rupture, myringotomy and those who were only antibiotically treated. The only notable point is that the patients with spontaneous rupture had a somewhat lower initial air conduction curve than the other two groups.

Neither could any differences be found between the audiograms of patients with different bacterial isolations (Figs. 6, 7).

Six patients as mentioned before had a residual secretory otitis media with large amounts of highly viscous transudate. The mean audiograms of these patients (Fig. 8) showed a more pronounced air–bone gap at all frequencies even at the first control, compared with the

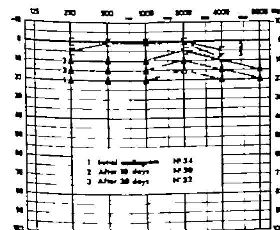


Fig. 6 Mean audiograms for the affected ear in patients with isolation of *Haemophilus influenzae*

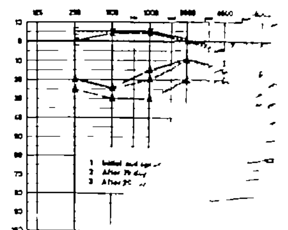


Fig. 8 Mean audio... patients with residu...

total material. The air–bone gap of these subjects was reduced slowly The hearing was normalized first after treatment with antihistamine and after myringotomy

DISCUSSION

The air conduction thresholds of patients with acute otitis media were only moderately elevated in the acute stage There were surprisingly small differences between the thresholds of those with bulging ear-drums (later myringotomized) and of those who were treated with only antibiotics. The initial air–bone gap was about 20–25 dB for all frequencies. The bone-conduction thresholds were all within normal limits and no sensorineural impairments appeared. After 10 days most of the patients had a normal hearing independent of the lapse of the otitis. The moderate to slight impairment and the rapid normalization of the hearing may be due to the short lapse of the otitis before therapy and the quick restitution of the mucous membrane of the middle ear mastoid and the Eustachian tube under adequate antibiotic treatment.

In an earlier paper on acute otitis media the patients were divided into three groups according to the therapeutic results (Herberts et al. 1971)

The audiograms of the therapeutic groups were compared. No major differences could be found between the patients with an uneventful healing and those regarded as "therapeutic failures"

ZUSAMMENFASSUNG

Ein nicht ausgewähltes Material von 136 Patienten mit Zeichen und Symptomen einer akuten Otitis Media sind audiologisch, bezüglich ihrer Luft und Knochenleitung untersucht worden. Diese audiologischen Untersuchungen sind während der Heilungsperiode in verschiedenen Zeitabständen wiederholt worden. Die erste audiologische Untersuchung wurde vor Beginn irgendeiner Behandlung vorgenommen. Es konnte keine Verschlechterung der Gehörnervsempfindlichkeit gemessen werden. Der Abstand der Meßwerte zwischen Luft und Knochenleitung war zu Anfang 20 dB derselbe schloß sich jedoch in den meisten Fällen im Laufe von 20 Tagen. Es konnte außerdem keine fortbestehende Verschlechterung des Gehörs registriert werden. Zwischen den Audiogrammen der Patienten, mit Spontaner Ruptur Myringotomy und nicht Myringotomy konnten keine großen Unterschiede festgestellt werden.

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MEDIASTINOSCOPIC OBSERVATIONS OF METASTATIC SPREAD IN PULMONARY CARCINOMA

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Abstract Mediastinoscopy was made in 338 patients with lung cancer and biopsies were taken from para tracheal, parabronchial and carinal lymph nodes. Positive biopsies were obtained in 159 cases (47 %). In 168 right lung tumors, metastases were found ipsilaterally in 49 % and contralaterally in 20 % Of 170 left lung tumors, 45 % showed metastases ipsilaterally and 25 % also on the contralateral side. Contralateral metastases from the right upper lobe were rare (7 %). Histologically epidermoid carcinoma showed the lowest number of metastases (34 %) while the microcellular anaplastic type had metastases in 81 % When the mediastinal lymph nodes become involved, curative surgery is very rarely useful and radio- or chemotherapy should be considered.

Rouvière s (1932) findings concerning the normal pulmonary lymph flow indicated that the flow from the right lung is directed straight to the tracheo-bronchial lymph nodes or to carinal nodes and from there to the paratracheal nodes. From the left side the lymphatic channels pass either to the tracheo-bronchial and anterior mediastinal lymph nodes, or to carinal and from there to the right paratracheal nodes. Consequently in malignant disease, metastases from the left side have been considered to occur frequently to the right whereas metastases to the left paratracheal nodes from the right lung are believed to be rare

In his extensive studies, Nohl (1962) and Nohl-Oser (1971) presented detailed data on metastatic nodes found in the resected specimens and at mediastinoscopy Nohl-Oser emphasized Borrie s concept (1952) that the lymphatic sump distal to the upper lobe bronchi is the main site of early metastases, from which area further spread occurs to the tracheo-bronchial and carinal nodes. In his mediastinoscopic examination of 316 patients with right-sided lung cancer metastases to the left occurred in 3 8 % whereas there was spread to the ipsilateral side in nearly 50 % In a total of 248 cases with carcinoma of the left lung, 24 % showed metastases to the regional tracheo-bronchial nodes and 15 % to the contralateral paratracheal nodes. Rouvière s data were thus confirmed in general. On the other hand, Greschuchna & Maassen (1971) reported a clearly higher incidence of metastatic spread from right to left, and in their series of 479 cases of carcinoma of the right lung, 11 % showed contralateral metastases. This spread most frequently (26 %) occurred from the middle lobe and least frequently (5 %) from the lower lobe. Contralateral tumors were found in 24 % of 427 cases with carcinoma in the left lung. They somewhat less frequently arose from the upper lobe than from lower lobe tumors (33 %).

Our earlier studies (Palva, 1964 Palva et al., 1968) of metastatic spread based on mediastinal biopsies were more in line with the data of Greschuchna & Maassen (1971). In this paper we will evaluate our findings in the present material of 338 cases of pulmonary carcinoma subjected to mediastinoscopy and lymph node biopsy from various sites during the period 1964–1971

Table I *Localization of primary tumor*

Histologic classification	Right lung: Main bronchus	Right lung: Upper lobe	Right lung: Middle lobe	Right lung: Lower lobe	Right lung: Total	Left lung: Main bronchus	Left lung: Upper lobe	Left lung: Lingula	Left lung: Lower lobe	Left lung: Total	Total
Anaplastic carcinoma											
Microcellular		10	7	4	21	4	15	3	8	30	51
Other	1	35	11	10	57	6	29	1	24	60	117
Epidermoid carcinoma	10	27	13	9	59	10	30	6	14	60	119
Adenocarcinoma		10		4	14	2	6	1	2	11	25
Alveolar cell carcinoma		1		3	4				1	1	5
Non-defined		6		7	13		6		2	8	21
Total	11	89	31	37	168	22	86	11	51	170	338

Figures referring to middle lobe include tumors of the stem bronchus.

MATERIAL AND RESULTS

Table I shows the localization of the primary tumors of the right and left lung compared with the histological type. The cases were classified into four groups by the site affected in each lung (main bronchus, three principal lobes), the lingular segments being listed separate from the upper lobe on the left side. Tumors arising in the right stem bronchus distal to the upper lobe bronchi down to the level of the upper rim of the superior lower lobe bronchus were included among the right middle lobe lesions.

Table II gives the number of positive and negative biopsies and the main method of treatment. The number of positive biopsies, 159 represented 47% of the total material. The majority of these patients (147) were treated conservatively. In 12 cases, operative treatment was attempted, but in none was a curative resection possible. In the 179 cases with negative mediastinoscopy operative treatment was the method mainly used (122 cases or 68%). In the remaining cases conservative treatment was adopted for a variety of reasons dur

Among the cases with negative biopsies there were 25 (14%) t ing mediastinoscopy

Table II *Findings at mediastinoscopy related to treatment*

	Tumor type: Anaplastic: Microc.	Anaplastic: Other	Epidermoid	Adenoca.	Alveolar	Non-defined	Total
Positive biopsy	39	63	39	13	1	4	159
Lobectomy	1	2	1	2			6
Pneumonectomy			2				2
Thoracotomy		1	2	1			4
Conservative treatment	38	60	34	10	1	4	147
Negative biopsy	12	54	80	12	4	17	179
Lobectomy	3	23	24	7	2		59
Pneumonectomy	5	12	25		1		43
Thoracotomy	2	5	6	2		5	20
Conservative treatment	2	14	25	3	1	12	57
Total	51	117	119	25	5	21	338

which carcinomatous lymph nodes were found at resection. However the majority of these were situated either in the lymphatic sump, or posterior or anterior to the mediastinoscopy level, or at the periphery. In 5 cases (3%) metastases were demonstrated in the area clearly accessible to the mediastinoscope.

Figs. 1 and 2 show metastatic spread from the areas indicated in Table I. From the right upper lobe, metastases to the right tracheobronchial area were the rule, 47 (53%) of 89 cases, but to the left they were very rare, totalling only 2 cases (2%). For metastases from the right main bronchus these figures were respectively 55% and 18%, from the middle lobe 48% and 26%, and from lower lobe carcinomata 41% and 14%. Metastasis to the contralateral side was thus considerably more frequent from the three other sites than from the upper lobe.

For the left lung, metastases to the right side arose more frequently from the main bronchus (5 cases or 23%) than from the upper (9 cases or 10%) or lower (5 cases or 10%) lobe. Ipsilateral metastases from the left upper lobe were just as common as on the right side (49%). Metastases from the lingular segments were found in this series on the ipsilateral side only (17%), but the series is small.

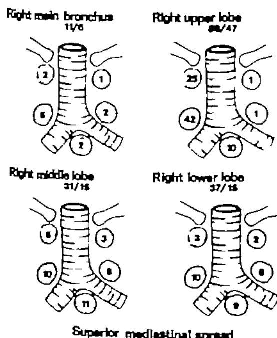


Fig. 1. Number and sites of malignant nodes discovered on mediastinoscopy in the right lung. Figures indicate the total number of cases and the number with metastatic nodes for each of the four parts.

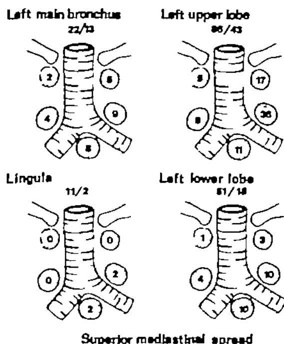


Fig. 2. Number and sites of malignant nodes discovered on mediastinoscopy in tumors of the left lung.

Figs. 3 and 4 relate metastasis to histological type of the tumor. Metastatic spread from the right side was least frequent in the case of epidermoid carcinoma (34%), adenocarcinoma metastasized in 50%, microcellular in 81%, whereas involvement of nodes by other anaplastic carcinomata occurred in 61%. Contralateral metastases were comparatively rare in cases of adenocarcinoma and epidermoid cancer (7% and 5% respectively), while the microcellular type showed contralateral spread in 19% and other anaplastic types in 14%.

Metastases from the left lung, from epidermoid carcinoma were also less frequent (32%) than from the other three types (microcellular 73%, other anaplastic 47%, adenocarcinoma 55%). Contralateral metastases occurred in all tumor types but here too epider

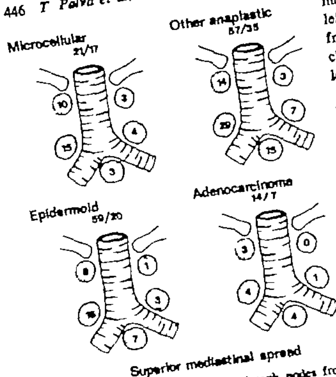


Fig 3 Distribution of infiltrated lymph nodes from tumors of the right lung in relation to histologic type of tumor

moid carcinoma showed the lowest figure (6%) the other types varying from 12% to 16%

Metastatic spread, demonstrated as positive mediastinal biopsies for the right and left lungs, is shown in Fig 5 Of the 168 right ung tumors, metastases were found in 83 cases (49%), and of these 17 (20%) showed metastases on the contralateral side. Of the 170 tumors of the left lung 76 (45%) had metastases and 19 (25%) of these had metastases to the contralateral right side.

COMMENT

The results of this series of 338 cases of lung cancer are in agreement with our earlier data and confirm the findings of Greschuchna & Maassen (1971) indicating considerable contralateral spread also from the right lung. In our cases this was slight from the right upper lobe lesions (2%) spread from the middle lobe and stem bronchus showing the highest figure (26%) and from the lower lobe an intermediate figure (14%) Metastases from the left lung towards the right occurred most often from the main bronchus tumors (23%) and clearly less often from the upper and lower lobes (10%)

Even admitting the general correctness of Rouvière s concept, it is a fact that metastatic spread from right to left occurs in a fai number of those cases in which the route fro the lymphatic sump leads to the carinal regio This must be taken into account particula when patients with cancer in the middle lower lobes are being evaluated for opera procedures.

It is clearly established by now that, metastases have extended beyond the lym ic sump representing stage 3 in the Sa Nohl classification there is a gener lymphatic system involvement. The dise pointed out by Nohl-Oser is not limited lymph nodes but involves the lymphat sels between them. This means that h of nodal involvement all lymphatic c

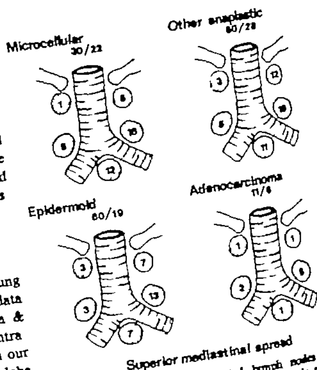
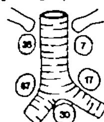
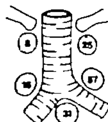


Fig 4 Distribution of infiltrated lymph nodes in tumors of the left lung as related to histologic type of tumor

Right Lung 168/83 cases Left Lung 170/78 cases





Superior mediastinal spread

Fig 3 Total number and sites of invaded lymph nodes found by mediastinoscopy in right and left lung carcinoma.

along the spread route must be infiltrated. It implies further as stated for instance by Nohl-Oser (1971), Palva (1964), Palva et al. (1968) Paulson & Urschel (1971) and by ourselves (1971) that resection, even though it might be technically possible is extremely seldom of benefit. Equally good or better results are achieved by modern radio- or chemotherapy without postoperative mortality and prolonged morbidity If resection is being planned, Kirschner's (1971) suggestion to give first a full dose of radiotherapy for eradication of the mediastinal disease, combined later with resection of the primary tumor may be valuable but has yet to be proved by a large enough series of cases.

ZUSAMMENFASSUNG

Mediastinoskopie wurde bei 338 Patienten mit Lungenkarzinom durchgeführt und Biopsien wurden aus den paratrachealen, parabronchialen und Bifurkationslymphknoten entnommen. Histologisch positive Befunde begegnete man in 159 Fällen (47%). Bei 168 Tumoren der rechten Lunge wurden ipsilaterale Metastasen in 49% und kontralaterale in 20 der Fälle gefunden. Für 170 Karzinome der linken Lunge lag die ipsilaterale Metastasenrate bei 45% und die kontralaterale bei 25%. Die kontralateralen Metastasen vom rechten Oberlappen waren selten (2%). Von den histologischen Typen zeigte das Plattenepithelkarzinom die niedrigste Metastasenhäufigkeit (34%) und das kleinzellige Bronchuskarzinom die höchste (81%). Bei Tumoren, die mediastinale Metastasierung zeigen, ist chirurgische Therapie sehr selten erfolgreich. Diese Fälle müsste man durch Bestrahlung oder Chemotherapie behandeln.

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THE NORMAL ELECTROMYOGRAM IN HUMAN CRICOTHYROID MUSCLE

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Abstract The electromyographic pattern in 17 crico- thyroid muscles of 13 healthy subjects has been deter mined. The EMG recordings were made with a con- centric needle electrode, recording area 0.03 mm² In the majority of the muscles there was continuous ac tivity during quiet breathing throughout the phases of respiration. Some motor units fired with a steady frequency whereas in the others the discharge fre- quency varied with the respiratory phases, some show- ing an increase during inspiration, others during ex piration. Some 20 motor unit potentials were identi- fied from each muscle and, in all, 338 motor unit potentials were analysed. Most of the action potentials were di- or triphasic. Polyphasic potentials occurred in 1% of the total number of potentials. The mean duration of the action potentials was 3.99 ± 1 40 ms. The incidence of potentials <2 ms in the whole material was 5 ,. and varied in individual muscles between 0 and 16 The mean amplitude was 394 μV e 10th and 90th percentiles were 150 μV and 800 μV respectively The maximal amplitude of the inter erence pattern during deglutition was usually in the range of 1 200–2 000 μV

As shown in previous studies of the electro- myographic pattern in vocal cord paresis (Hag- lund et al., 1970 1972) neurogenic lesions may be established by several different criteria, viz. an increased incidence of potentials of short or long duration, a high frequency of potentials with high amplitude or an altered incidence of polyphasic potentials, as well as changes in the interference pattern during phonation or deglu tition Thus, in order to establish electromyo- graphic criteria that may facilitate diagnosis in cases of disturbance of motor functions of the larynx, a rather extensive knowledge of the variability in duration, amplitude and shape of the motor unit potentials of healthy muscles is needed. Such data from recordings in the vocal muscles are available (Knutsson et al, 1969) and have been the basis for electromyo- graphic investigations in cases of traumatic paresis of the recurrent nerve (Haglund et al, 1970) and of idiopathic vocal cord paresis (Haglund et al., 1972).

The motor control of the laryngeal muscles is exercised by the recurrent and the superior laryngeal nerve, the latter innervating only the cricothyroid muscle. To render possible a more complete evaluation of motor disturb- ances in the larynx, a determination of the electromyographic pattern in the cricothyroid muscles should therefore preferably be added to the studies of the electromyographic activity of the vocal muscles. A conclusive evaluation of possible lesions in the cricothyroid muscles of patients with voice disturbances is, however hampered by the lack of sufficient data to al- low an estimation of the significance of elec tromyographic findings, since only the mean duration of samples of few potentials from in- dividual muscles are known (Faaborg-Ander sen 1957). The present study of shape, ampli- tude and duration of a significant number of motor unit potentials, from each of a series of healthy muscles was therefore undertaken. The resulting data provide a basis for the use of electromyography in the diagnosis of neuro-

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genic lesions in the superior laryngeal nerve. As will be shown in a separate paper they facilitate evaluations of the pathogenesis of voice disturbances of unknown origin.

MATERIAL AND METHOD

Seventeen muscles from 13 healthy individuals were examined. The group consisted of 5 men and 8 women of mean age 31 years (range 23–63 years). None of the subjects had any previous history of voice disturbance. Indirect laryngoscopy was performed in all subjects and revealed a normal position and normal motility of the vocal cords.

Electromyographic recordings were made with a concentric needle electrode (Disa type 9013 K 32, needle length 43 mm, outer diameter 0.65 mm, leading-off surface of the platinum core 0.03 mm² and bevel angle 15°). The recordings were made between the centre core and the outer needle. A chest electrode placed between heart and larynx connected the subject to earth. The recordings were fed to a differential amplifier with an input impedance of 3 megohms and an essentially linear frequency response between 4 Hz and 10 kHz. The output was connected to an audiomonitor and a loudspeaker as well as to an oscilloscope. The potentials were photographed on moving film, from which all measurements were made. Analyses of shapes, durations and amplitudes of the action potentials were made only when at least 2 identical recordings from the same motor unit were obtained and the onset and end of the potentials could be well defined.

In order not to interfere with the action potentials to be recorded, no kind of anesthetic was given to the subjects. Nor did they receive premedication. The skin was pierced in the midline over the cricoid arch at the level of its superior margin. The tip of the needle was inserted until it made contact with the perichondrium. The needle was then directed laterally and slightly upwards and was allowed to follow over the cranial margin of the cricoid arch laterally. It was sometimes possible to feel the medial margin of the cricothyroid muscle with the palpating hand, and often also to feel when the needle penetrated the muscle. This mode of inserting the electrode enables an exploration to be made of a large portion of the muscle. Unintentional recordings from the sternothyroid and sternohyoid muscles were avoided by bringing the needle into immediate contact with the perichondrium of the cricoid arch. When the needle penetrates the cricothyroid muscle, the oscilloscope beam displays a muscle activity pattern. Motor units were identified by carefully advancing and rotating the needle. The needle was never advanced further than 10 mm into the muscle, but sometimes several insertions were made. By this method it was possible as a rule to identify at least 20 motor unit potentials from each muscle investigated. The subjects did not feel any pain when the muscles were explored, but experienced a certain discomfort when the needle touched the perichondrium. None of the subjects have noticed any degree of hoarseness since the examination. On the day following the exploration some of them felt a transient tenderness in the investigated muscles, which was most prominent during swallowing. Otherwise no discomfort was experienced.

RESULT

Activity pattern

The activity in the muscle was studied both during quiet respiration and during activation. During quiet breathing there was continuous activity in the cricothyroid muscle in 12 of the subjects investigated in spite of every effort to achieve relaxation (cf. Weddell et al., 1944; Faaborg-Andersen, 1957). Some motor units fired at a steady frequency, whereas the frequency of others varied with the respiration. Some of the latter motor units were active only during one of the respiratory phases, while others fired continuously modulating their frequency with the respiratory rhythm. Most units fired with a frequency of 10–20 per sec. The highest rate observed was 33 per sec. In

one subject however no activity was observed except during slight voluntary activation.

In most electrode positions the activity from different motor units within the pick up area of the electrode caused disturbances of the baseline, so that difficulty arose in distinguishing the individual motor unit potentials. However often a small movement of the electrode in the form of rotation gave a position where the background activity was small enough to permit separate motor unit potentials to be identified. Sometimes more than one motor unit potential could be identified in one and the same position of the electrode.

In initial examinations it was found that during phonation the maximal amplitude and the degree of interference varied in repeated activations. Successive deglutitions more often gave a complete interference pattern of constant and usually higher amplitude (cf Faaborg-Andersen, 1957) Deglutition was therefore used in the following examinations to obtain a standard activation. The activations thus accomplished regularly caused an interference pattern, the maximal amplitude ranging between 1 200 and 2 000 μV in the different muscles tested.

Shape duration and amplitude of the action potentials

A study was made of 338 potentials from 17 muscles in 13 subjects. Seventy-seven per cent of the potentials were di- or tri-phasic and 19% monophasic 3% were tetraphasic. Only 4 potentials with more than 4 phases, classed as polyphasic, were present in the whole material, constituting 1% of the total number of potentials recorded. These polyphasic potentials had an amplitude range of 220–1 000 μV and their duration varied from 3 75 to 5 75 ms.

Of the potentials with one to four phases 28% to 47% showed some degree of notching. The incidence of potentials with a certain number of phases varied widely among different muscles. Monophasic potentials appeared in 5% to 46% of the total, diphasic in 23% to 82% triphasic in 3% to 50% and tetraphasic in 0% to 12% The incidence of polyphasic potentials varied from 0% to 4%

Fig 1 Histogram showing the distribution of the duration of 338 action potentials recorded from 17 normal cricothyroid muscles.

The distribution of the duration of the 338 potentials is given in Fig 1 The figure shows a fairly even distribution and it has been considered reasonable to use statistical parameters for the normal distribution curve to describe the durations of the total population of potentials identified. Thus, the mean and standard deviation of the total number of potentials was 3.99±1 40 ms. In individual muscles the mean varied from 3 11±0 64 ms (*n* 19) to 4 67±2.35 ms (*n* 24). The incidence of potentials with a duration <2 ms was 5% in the whole material In individual muscles the incidence varied between 0% and 16%

The amplitudes were measured in the same 338 potentials. Thirty-one per cent of the potentials were of magnitude 150–250 μV The mean of all potentials was 394 μV In individual muscles the mean varied from 230.0 μV (*n* 23) to 771 4 μV (*n* 28) The low mean amplitude was found in the subject lacking activity in spontaneous breathing. Among the others a low mean amplitude was found in those with low degree of activity during quiet breathing. Apparently a potential has to be quite large to permit its identification when there is continuous resting discharge, whereas even potentials of low amplitude may be easily identified against background discharge of low level. Consequently the large variation in amplitude might to a certain extent be a consequence of the sampling procedure. In Fig. 2 the ampli-

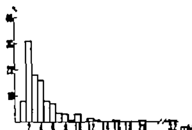


Fig. 2 Histogram showing the distribution of the amplitudes of 338 action potentials recorded from 17 normal cricothyroid muscles.

tudes of all potentials have been plotted. As will be seen the distribution is skew On account of this it has been considered more reliable to describe the 10th and 90th percentiles as a basis for later evaluations of pathological conditions. The 10th percentile has been calculated to be 150 μV and the 90th to be 800 μV and it follows that 80% of all potentials had amplitudes within this range. In 15 of the 17 muscles tested more than 80% and in the remaining 2 muscles between 70% and 80% of the potentials had amplitudes within the range 150–800 μV This range therefore seems to give a fairly good estimate of the normal amplitude distribution.

In the diagnosis of neurogenic disorders the occurrence of fibrillation potentials is an important finding. These potentials usually have a short duration and a low amplitude (cf Buchthal & Rosenfalck, 1966). Potentials of short duration occur also in normal laryngeal muscles and a special study of potentials with a duration <2 ms was made in the present material. Eighteen potentials were found comprising 5.3% of the total number Their amplitudes were usually in the range 100–300 μV

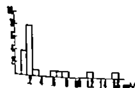


Fig. 3 Amplitude distribution of action potentials of duration 2 ms or less recorded from normal cricothyroid muscle. Ordinate number of potentials.

but potentials with a much higher amplitude were also found. In Fig. 3 the amplitudes of all potentials <2 ms have been plotted. As will be seen, the distribution of these potentials shows a resemblance to that of the amplitudes of all potentials.

DISCUSSION

Earlier investigations have pointed to the difficulty of recording and measuring single motor unit potentials in human laryngeal muscles owing to their sustained activity (Weddell et al. 1944) which causes baseline disturbances and prevents a distinction to be made of the onset and end of a motor unit potential. Such sustained activity was an almost regular observation in the present investigations, but the difficulties in identifying action potentials could usually be reduced through minute alterations in the position of the needle electrode whereby motor unit potentials with less background disturbance could be recorded.

In electromyographical recordings from different points in the same muscle the duration amplitude and shape of the action potentials may vary (cf Buchthal & Clemmesen 1941 Petersén & Kugelberg, 1949 Buchthal et al. 1954). In this investigation recordings were made with the tip of the needle in many different positions to sample at random potentials from different sites within the muscle. Care was taken to identify about 20 motor unit potentials in each muscle to obtain a statistically significant number of potentials for analysis.

The recording procedure used enabled a study to be made of several motor unit potentials during repeated respiratory periods. Thus, there were motor units with constant discharge frequency and others which modulated their frequency with the respiration. Some motor units had a maximal discharge frequency during the inspiratory phase, others during the expiratory The presence of inspiratory and expiratory motor units accords with findings made during recording of motor unit

potentials in the cricothyroid muscle of the cat (Rudomin 1966) and vocal muscle of man (Knutsson et al. 1969). In studies of the total electromyographic activity during respiration an increase of the activity has been observed both during the expiratory (Fink et al. 1956) and during the inspiratory phases (Faaborg-Andersen 1957).

In the present investigation the mean duration of the motor unit potentials was found to be 3 99±1 40 ms (S.D *n* 338), while in the only investigation earlier performed the mean duration was 5.3±0.1 ms (S E. *n* 201 Faaborg-Andersen 1957) The mean duration of motor unit potentials as recorded with diffe rent types of electrodes varies (Petersén & Ku gelberg 1949) The difference in mean dura tion found in the present investigation and in that of Faaborg-Andersen is, however not possible to explain in this way Similar types of electrodes were used in both investigations the only difference being the outer diameter of the cannula. Such a difference in size of con centric needle electrodes does not affect the duration of recorded action potentials (Buchthal et al. 1954). However the difference in mean age may at least in part explain the dif ference in mean duration, since the mean du ation of the motor unit potentials in a muscle increases with increase of age (Petersén & Kugelberg. 1949· Sacco et al. 1962) Thus, the mean age of the subjects in the present study was 31 years and of those studied by Faaborg-Andersen between 50 and 56 years. By way of comparision it may be stated that the mean duration in the vocal muscle in age groups 20–30 and 40–60 years was 3 43 ms and 4.21 ms, respectively Also the difference in sampling of potentials may explain part of the difference in mean value of the duration In the present investigation a sampling of motor unit potentials from many sites were made while in the investigations of Faaborg Andersen only few potentials from a single place within each muscle were recorded.

The mean duration of the motor unit potentials in the vocal muscle was 3 76±1 11 ms (*n* 469· Knutsson et al. 1969). The difference between the values found in the vocal and in the cricothyroid muscle is small but statistically significant. Compared with the mean duration of potentials in limb muscles the durations of the potentials in the cricothyroid muscle are considerably shorter and could be placed in the same group as the vocal muscles, the extraocular muscles and the facial muscles.

When explaining differences in duration of motor unit potentials the longitudinal spread of the end plates of the motor unit and the consequent variation in distance which must be travelled by the muscle spikes before reaching the recording electrode has been shown to be an essential factor (Buchthal et al. 1955). In the cricothyroid muscle the motor end plates are localized to a narrow band in the middle of the muscle comprising about 15% of its length (Faaborg-Andersen, 1957). The total length of the cricothyroid muscle is 15 mm and the temporal dispersion of the muscle fiber spikes when arriving at the recording electrode with a velocity of about 4 m/sec must be comparatively small. This small temporal dispersion explains the short durations of the motor unit potentials found in the cricothyroid muscle.

The incidence of polyphasic potentials varies in different muscles. Thus, in normal limb muscles 2–4% of the potentials have more than 4 phases. In the facials muscles their frequency is still higher (Petersén & Kugelberg, 1949) whereas no polyphasic potentials have been found in normal extraocular muscles (Björk & Kugelberg 1953). In single vocal muscle polyphasic potentials are present in up to 15% whereas in normal cricothyroid muscle up to 4%

The present investigation reports data which constitute the main elements of the normal electromyographic pattern in the cricothyroid muscle and should provide a basis for a more complete electromyographical evaluation of laryngeal functions than previously possible. Thus, it may be used in motor disturbances of the vocal cord. In a series of electromyographical examinations (Haglund et al., 1970,

1971) it has been shown that a partial paresis of the recurrent nerve may exist although the laryngoscopic examination reveals a normal motility of the vocal cords, thus indicating that conventional methods cannot always reveal a partial paresis. In a subsequent paper examples of the deviations from normal electromyographic pattern in the cricothyroid muscle in some different types of lesions will be given.

ZUSAMMENFASSUNG

An 13 gesunden Menschen wurde das elektromyographische Muster von 17 cricothyroiden Muskeln studiert. Die EMG-Untersuchungen wurden mit einer konzentrischen Nadelelektrode durchgeführt. Bei ruhiger Atmung war bei der Mehrzahl der Muskeln eine gleichmässige Aktivität während der Phasen der Respiration vorhanden. Einige motorische Einheiten entluden sich mit gleichmässiger Frequenz, wogegen bei anderen die Entladungsfrequenz je nach der Respirationsphase wechselte. Einige zeigten eine Zunahme der Aktivität während der Inspiration, andere dagegen bei der Exspiration. Etwa 20 Potentiale der motorischen Einheiten wurden von jedem Muskel erhalten. Die Mehrzahl der Potentiale waren di- oder triphasisch. Polyphasische Potentiale erhielten wir bei 1% der gesamten Anzahl der Potentiale. Die mittlere Dauer der Potentiale war 3,99 ± 1 40 ms (n = 338). Das Vorkommen von Potential < 2 ms betrug im ganzen Material 5% und variierte in den individuellen Muskeln zwischen 0–16%. Die mittlere Amplitude war 394 µV (n = 338). Das zehnte und neunzigste Perzentil betrug 150 µV bzw 800 µV Die Maximalamplitude des Interferenzmusters lag gewöhnlich zwischen 1 200 und 2 000 µV

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ECHO GLOTTOGRAPHY

Ultrasonic Recording of Vocal Fold Vibrations in Preparations of Human Larynges

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Abstract Except for the entirely subjective strobo- scopy there is no generally accepted clinical method for continuous recording of vocal fold vibrations. In laryngology and phoniatrics it is therefore usually difficult to assess vocal fold function objectively Echoglottography however an ultrasonic pulse-echo method for the study of the vibrating vocal folds, meets many of the necessary requirements.

For the recording of vocal fold vibrations a special, highly sensitive ultrasound reflectoscope has been constructed, allowing the use of transducers with dif ferent ultrasound frequencies. A pulse repetition fre- quency of 10 kHz was chosen, sufficient for con tinuous recording of fast vibratory movements, yet giving an adequate recording depth. In initial experi- ents an ultrasound frequency of 4 MHz was shown penetrate even ossified cartilages, this frequency ing high enough for high longitudinal and lateral resolution of the ultrasound beam.

As a basis for the development of an echoglotto- graphic method the ultrasound echoes from laryngeal specimens have been recorded Echoes from the free margin of the vocal folds could be demonstrated and unequivocally identified. Vibrations in these same structures gave rise to characteristic curves, resembling glottograms recorded with other less convenient methods.

The vibratory pattern of the human vocal folds during phonation is of great interest in laryngeal physiology as well as in clinical laryngology Because of their high frequency the vibrations of the folds cannot be visualized directly but during recent decades several methods have come into use to overcome this obstacle. However since all of these more or less indirect methods have certain drawbacks, none of them has been generally adopted in clinical routine work at departments of la- ryngology

The commonest clinical method is synchron- stroboscopy described in detail by Schönhärl (1960). It provides no objective recording but is entirely dependent on the investigator's sub- jective impression of slow motion which ap- pears when the human eye observes very short flashed images from consecutive vibratory cycles, and no continuous recording of the vibrations can be made. A great deal of re- search work on laryngeal physiology has been done with high speed film technique, first described by Farnsworth (1940) but in spite of isolated reports to the contrary (Teter et al, 1969), it must be said to be too expensive and too space and time-consuming for use in clinical routine. Besides, the employment of a fixed laryngeal mirror as part of this method demands a great deal of cooperation from the subject.

Untrained patients, who in addition, may present pharynx and larynx with narrow anat omy are therefore difficult to photograph.

A comparatively easy way to record the

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continuous variations of the glottal area during phonation is by photoelectric glottography (Sonesson, 1960). By this method the intensity variations of a transilluminated light beam directed through the glottis are recorded and visualized as a curve on a cathode ray oscilloscope. However the method does not allow conclusions concerning the vibratory movements of one single vocal fold, and some authors have pointed out that it yields insufficient information about certain parts of the vibratory cycle (Köster & Smith, 1970).

In electroglottography described by Fabre (1957) the impedance variations in the tissues of the neck are recorded during phonation. Because of variations in tissue impedance not dependent on vocal fold movements, this method involves a considerable risk of artefacts interfering with recording (Frøkjaer Jensen, 1969)

In studies of laryngeal function many investigators have used acoustic analyses of the emitted voice, such as sound spectrography (Nessel, 1962; Yanagihara, 1962, 1967) or inverse filtering (Fant, 1961). In addition to other disadvantages of these methods in clinical work, only limited conclusions can be drawn from them as regards the vibratory pattern of each vocal fold.

It is obvious from these introductory remarks that an ultrasonic method for recording of vocal fold vibrations would be very convenient in clinical laryngology and phoniatrics, and it would also be very comfortable for the patient. The recording would be continuous, direct and objective—a combination not possible to achieve by any other single method. Besides, it would be possible to develop the method by using two transducers covering both vocal folds simultaneously

The first to present an ultrasonic recording of a vibrating vocal fold was probably Mensch in 1964 Unfortunately his traces do not allow any analysis of the vibratory movements involved. In two almost identical papers Kitamura et al. (1968) have published very interesting recordings, and their forthcoming more detailed report is eagerly looked forward to Hertz et al. (1970) have presented a preliminary report on vocal fold recordings, prepared at our laboratory with an apparatus originally devised for echocardiography This type of apparatus has a pulse repetition frequency of 1 000 Hz, which is not high enough to produce clinically usable recordings of vocal fold vibrations with a frequency of 100 Hz or more.

Therefore an ultrasonic reflectoscope has been constructed with a pulse repetition frequency of 10 000 Hz, which has proved to give satisfactory recordings of vocal fold vibrations. An outline of this new apparatus is given below Technical details will be given in a special report to be published later

PHYSICAL PROPERTIES OF ULTRASOUND

Before the technical data and the application of the ultrasonic echo method for studying the vibrating vocal folds are described, a very short description of the physical properties of ultrasound will be presented below and illustrated in Fig. 1 For more detailed information the reader is referred to Hertz (1967).

Reflection

When a plane acoustic wave travelling in a medium impinges upon a boundary of a second medium, part of the wave is reflected into the first medium. The reflected sound intensity I resulting from a sound beam of intensity I_0, falling perpendicularly on a flat surface, is represented by

$$I = I_0 \left(\frac{\rho_1 c_1 - \rho_2 c_2}{\rho_1 c_1 - \rho_2 c_2}\right)^2$$

where ρ and v are densities and sound velocities in two media on each side of a reflecting boundary (see Fig. 1 *a*). As the larynx is filled with air having an acoustic impedance, $\rho\, v$ which is much smaller than the surrounding tissues, strong reflection from the boundary vocal fold vs. air is to be expected.

Absorption

The absorption of ultrasound is considerable in biological tissue. If a parallel ultrasound beam travels through a certain medium the intensity of the beam decreases along the beam according to the relation

$$I = I_0 e^{2kfx}$$

where k is a constant depending on the biological substance, f the sound frequency and x the distance covered by the sound wave in the medium. This phenomenon is illustrated in Fig. 1 *b* It appears from this that ultrasound of very high frequency is too much absorbed to be of practical use.

Diffraction

An ultrasound beam like any wave motion diverges because of diffraction. In the well-known Fraunhofer diffraction formula, $\sin \varphi = 0\ 61\ \lambda/\alpha$, the angle φ is the divergence angle, λ is the wavelength of sound and α the radius of a circular transducer From this it is obvious that the use of a very high frequency (short wave length, λ) will result in a small diffraction angle and thus in a well defined beam. The diffraction is illustrated in Fig. 1 *c* It is important to notice that a small transducer may generate a poorly defined beam with a high divergence angle.

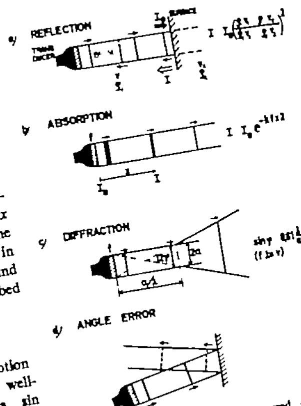


Fig 1 Physical properties of ultrasound. — transmitted ultrasound pulse --- reflected ultrasound pulse. (*a*) Reflection of ultrasound beam towards a surface where ρ and v are densities and sound velocities in two media on each side of a reflecting boundary (*b*) Absorption of ultrasound, where k is a constant depending on the biological tissue, f the sound frequency and x the distance covered by the sound. (*c*) Diffraction of an ultrasound beam. In the formula φ is the angle of divergence, λ the wavelength of sound in the medium and α the radius of a circular transducer (*d*) Angle error Loss of echo when beams do not strike reflecting surface at right angles.

Angle error

If the reflecting surface is not perpendicular to the transmitter a great deal or all of the transmitted sound will not be reflected back to the transducer Fig. 1 *d*.

METHOD

Technical principles

The ultrasonic pulse echo method is used for recording of vocal fold vibrations. The movements of the ultrasound echoes are recorded by the time motion (TM) technique well known from echocardiography Fig 2 shows the principle of the time motion technique A saw tooth voltage generated from the ultrasound reflectoscope deflects the electron beam in a cathode ray tube (CRT) along the negative y-axis for every transmitted ultrasound pulse. At the same time the intensity of the electron beam in the CRT is modulated by the echo signal from the reflectoscope in such a way that it appears on the CRT screen only when an echo is received. If the time base (x-axis) of the cathode ray oscilloscope runs at a suitable slow deflection speed, the movements of the vocal fold echoes can immediately be observed on the screen. For

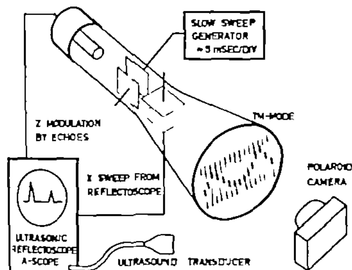


Fig. 2. Principal diagram of the TM recording method in which the echoglottographic recording of the vibrating vocal folds are directly displayed on the screen of a cathode ray tube and photographed with a Polaroid camera.

registration and filling the CRT-screen is photographed with a polaroid camera.

Reflectoscope

As mentioned above, commercial ultrasound reflectoscopes with a pulse repetition frequency of 50–1 000 Hz are useless because of the rapid vibratory movements of the vocal folds. Therefore the new ultrasound reflectoscope was built so as to yield a pulse repetition frequency of 10 000 Hz and was especially adapted for recording of the movements of the vocal folds. A block diagram of the apparatus is shown in Fig. 3.

The reflectoscope consists fundamentally of five blocks. The first block, a 10 kHz clock pulse generator controls the function of the following three blocks: sweep-generator transmitter and depth compensation generator. The fifth block is the receiver unit with inputs from the transducer and the depth compensation generator and an output to the oscilloscope (TEK. 549) on which the TM-display is obtained. For control purposes, an A-scope display is achieved on a separate monitor oscilloscope.

The 10 kHz clock triggers the transmitter which generates 300 V pulses for the ultrasound transducer of only 1.0 μsec duration. This has the advantage of permitting the connection of transducers of different sizes and ultrasound frequency.

The 10 kHz clock also initiates the sweep generator which generates a saw tooth voltage each time an ultrasound pulse is transmitted. The start as well as the slope of the sweep can be adjusted. This makes it possible to select and magnify interesting echoes for TM display.

By the depth compensation generator losses due to ultrasound absorption in tissue can be neutralized within wide ranges.

The preamplifier of the receiver consists of five cascode amplifiers (Valley & Wallman, 1948) with overload protections. Cascode amplifiers have been chosen because of their excellent ability to amplify signals of very high frequency. The gain of this preamplifier is controlled by the depth compensation generator. Field effect transistors located near the cascode circuits ajust the gain of the receiver. They are operated by remote control which prevents the risk of undesirable oscillations.

For rectification, a new high-sensitive full-wave detector has been constructed. The rectified intensity modulation signal is transferred from a low impedance source via a coaxial cable to an amplifier placed immediately at

the cathode ray oscilloscope. This eliminates signal losses in the coaxial cable.

For TM representation of the vocal fold movements a storage oscilloscope is used. Because of the very high writing speed necessary a Tektronix 549 storage oscilloscope had to be chosen. The auto erase function of this CRO also makes it possible to discard less interesting echoglottograms, which saves time and film costs.

Depending on the fundamental frequency of the vocal fold vibrations (100–200 Hz) the time base of the oscilloscope is used at a deflection speed of 1–10 msec/div

The small size of the vibratory movements of the vocal folds puts the apparatus capacity for resolution to a severe test. The present equipment has experimentally been shown to measure correctly movements of 0.1 mm and less.

As the pulse repetition frequency is as high as 10 000 Hz, the silent period between two consecutive pulses has a duration of only 100 µsec. This is the time in which returning echoes must be received. As the sound velocity in the tissues is about 1 500 m/sec, the maximum recording depth is calculated at somewhat more than 7 cm. At higher pulse repetition frequencies the recording depth decreases and there is a risk of receiving ghost echoes from earlier pulses.

Transducer

To be able to resolve the complex movements of the vocal folds, a very narrow ultrasonic beam must be used. Therefore the crystal must be selected with great care. A large crystal produces too wide a beam, a small crystal a beam of increasing angle of divergence. These problems are discussed extensively by Edler (1961). As one solution, ultrasound of as high a frequency as possible has been used, the frequency being limited by the sound absorption. Transducers with the frequencies 2, 4 and 6 MHz have been tested.

The transducer crystal is made of a ceramic material which converts an electrical voltage into sound pressure (pulse transmitter), and sound pressure to an electrical voltage (echo receiver). The material in the transducer (Brush Clevite PZT 5A), a modified lead zirconate titanate strikes a mean between transmitting efficiency and receiving sensitivity for the transducer together with a relatively high mechanical damping. To prevent the transducer from "ringing" it is necessary to mount the ceramic bowl or dish on a backing material which will increase the damping of the disc appreciably. This backing material consists of fine tungsten powder imbedded in Araldite resin which efficiently scatters and absorbs the sound transmitted into it. The amount of tungsten powder is chosen in such a way that the acoustic impedance of the material is about the same as that required by the transducer to reach optimum damping.

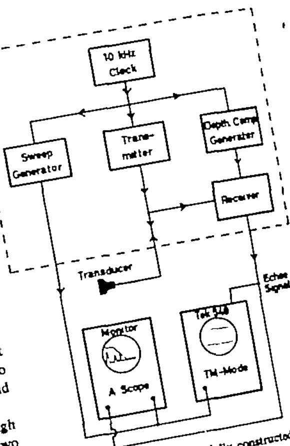


Fig. 3. Block diagram of especially constructed reflectoscope for echoglottography including a monitor oscilloscope for A-scop. and a storage oscilloscope for TM-display.

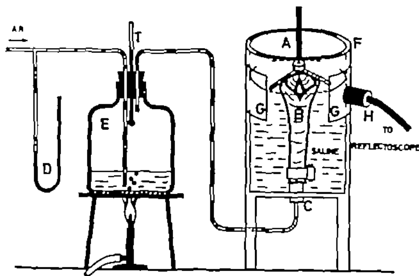


Fig. 4. Arrangement of experiments. Moist and heated air passes through the trachea of a laryngeal preparation suspended in a saline-filled vessel with windows for the transducer.

With this transducer and external electrical damping it is possible to achieve sound pulses as short as 1 μsec at 4 MHz.

Arrangement of experiments

In preliminary experiments ultrasound penetration of human thyroid cartilage with varying degree of ossification was compared with roentgenograms.

The arrangement shown in Fig. 4 was used for the principal part of our work. On a fork like stand (A) the upper part of a human larynx preparation (*B*) was fixed, so that the trachea was suspended vertically and could be connected to a plastic tube (*C*) for humidified and heated air (*E*). The temperature and pressure of the air could be measured by a thermometer (*T*) and a water-manometer (*D*) respectively. At certain air pressures and by manipulation of the laryngeal cartilages the vocal folds of the larynx preparation could be made to vibrate, emitting sounds of different pitch and quality. The larynx preparation was inserted into a circular perspex tank (*F*) with physiological saline or water. Windows (*G*) were cut in the tank and covered with a thin rubber membrane for application of the ultrasound transducer (*H*).

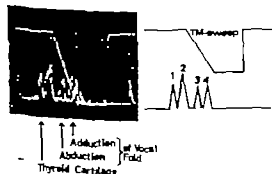


Fig. 5. Ultrasound registration of manipulations with a vocal fold. A-scope. Double exposure with representation of the echoes from the same vocal fold in abducted and adducted position respectively. *1.* External lamina, 2, internal lamina of thyroid cartilage; 3 vocal fold in abduction; *4.* vocal fold in adduction.

The experimental arrangements were made according to the principles developed by van den Berg et al. (1959).

RESULT

The ability of ultrasound to penetrate cartilage with varying degree of ossification was studied by measuring the amplitude attenuation at different frequencies. The results are shown in Table I. Measurements were made at the anterior edge and at the centre of four equally thick thyroid laminae varying in age and sex. The attenuation proved to be in good agree

Table I *Attenuation of ultrasound intensity due to absorption in thyroid laminae (measured in dB = –10 log I_0/I)*

Age/Sex	83/male		43/male		75/female		63/female	
Transducer frequency MHz	Anterior edge (–dB)	Centre (–dB)	Anterior edge (–dB)	Centre (–dB)	Anterior edge (–dB)	Centre (–dB)	Anterior edge (–dB)	Centre (–dB)
2	30	6	36	18	10	4	23	6
4	36	16	40	19	20	6	26	10
6		26		21	25	11	29	16

Very high absorption, not measurable with the technique used.

ment with the ossification as it appeared on an X ray from the cartilages. As expected from textbook information about the progression of larynx ossification due to age and sex (e.g. Lanz & Wachsmuth 1955) absorption was shown to be least in the central part of the thyroid cartilage

The human vocal folds are comparatively small structures: the size of their lateral excursion during vibration is often less than 1 mm Therefore the best possible resolution is demanded from the ultrasonic apparatus This can be achieved with ultrasound of high frequency But, as pointed out earlier the higher the frequency the greater the absorption, and there is a frequency limit when it becomes impossible to penetrate the tissues under investigation

In our experiments the sound beam was in some cases practically entirely absorbed by the thyroid cartilage at a frequency of 6 MHz. The ultrasound frequency of 4 MHz was found to be the highest possible for experiments with larynx preparations, and the present work was carried out mainly with a transducer of this frequency

At the beginning the experiments with larynx preparations were carried out without vibrations of the vocal folds. An echo representing the inner and outer surface of the thyroid laminae of the preparation and another representing the free margin of the vocal fold were demonstrated on the monitor oscilloscope (A mode) This latter echo was unequivocally identified by the insertion of a thin metal needle under the marginal mucosa of the fold, which resulted in a change of the previously demonstrated echo. Further the echo could be identified by a good correspondence between the distance displayed on the CRT and the actual distance from the transducer to the free edge of the investigated vocal fold.

Manipulation of the fold, resulting in adduction and abduction movements, were followed as corresponding movements of the previously identified echo on the monitor whereas the remaining echoes did not move (Fig. 5). These slow movements of high amplitude were also demonstrated by TM recording as an undulating curve (Fig. 6).

When the vocal folds were made to vibrate by application of the moist and heated air stream, the excursions of the echo on the

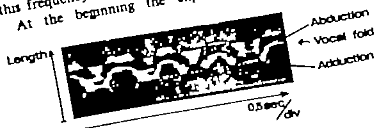


Fig 6 Ultrasound registration of manipulations with a vocal fold. TM-display. The slow ab- and adductory movements of the vocal fold are represented by an undulating curve

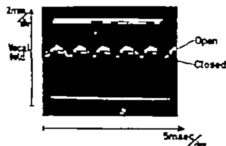


Fig. 7. Echoglottogram of vocal fold vibrating at 110 Hz. Note similarity of curves with the vibratory pattern well-known from high-speed films and photoglottography. The closed, opening- and closing phases can clearly be distinguished.

monitor were of course too fast for the naked eye to follow and could only be perceived as a blurring of the vocal fold echo. By TM display however it was clearly possible to get distinct curves from the vibrating folds (Fig. 7). As seen from the figure, the repetition frequency of about 10 kHz was sufficient to give a continuous representation of vocal folds, vibrating at about 110 Hz.

DISCUSSION

Beach & Kelsey (1969) seem to be the only investigators who have correlated an ultrasonic vocal cord recording with another sort of recording. They compared ultrasound Doppler signals from the region of the vocal folds with the actual vibratory phase as it appeared on the frames of a high-speed film. Velocities and displacements calculated from the Doppler signal did not always correlate well with the motions of the folds and the Doppler monitoring system proved unsatisfactory. It remains to be seen if this conclusion is valid also for the pulse echo method used in this paper. However, we do not find this very probable in view of the data presented in this report. The complex vibratory movements of the vocal folds with continuously changing surfaces act as sources of multiple echoes which merge into a single Doppler signal. Its integrated velocity curve is not correlated with the motion of any actual part of the vocal fold surface. These problems do not arise with the present method as multiple echoes are not integrated but displayed separated in time. This means that the distance to the echo-emitting structure can be accurately determined and that the most relevant echo can be distinguished.

Unlike earlier authors, we have not confined ourselves to obtaining curves from out

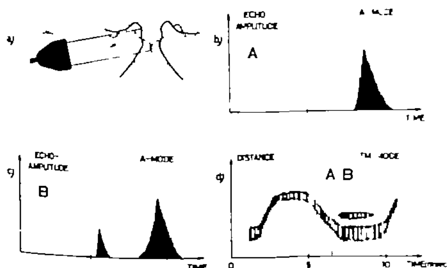


Fig. 8 a–d. Two diagrammatical frontal sections, *A* and *B* showing the complex and changing vocal fold surface during vibration (*a*), sometimes causing multiple and irregular echoes displayed in A-mode (*b* and *c*) as well as in TM-mode (*d*).

side the neck. Instead, this paper is meant to be the first report on a systematic development of the method. In studies of laryngeal specimens we have been able to locate the echo-evoking structures directly in the larynx. Further TM-displayed curves have been correlated to slow abductory and adductory movements as well as to vibrations of this same structure i.e. the vocal fold.

In initial experiments we tried to apply the transducer directly to the thyroid cartilage of the preparation. These attempts failed as the echoes from the laryngeal structures were overshadowed by the start pulse because of the short distance. Therefore the larynx preparations were suspended in a vessel filled with water or saline.

In a special study we analysed the ability of the echo to penetrate the laryngeal cartilages when these are more or less ossified. Earlier experience, e.g. from echo-encephalography (Jeppsson, 1961) has shown that cancellous bone can absorb ultrasound to a very high extent. It showed possible to solve this problem by the use of a suitable ultrasound frequency and by directing the ultrasound beam perpendicularly to the glottis and against the central parts of the thyroid cartilage.

In our opinion the greatest difficulty is bound up with the complex movement pattern of the vibrating vocal folds, earlier commented upon by Beach & Kelsey (1969) and described in detail by Schönhärl (1960) in his excellent monograph on laryngeal stroboscopy. The vibratory movements do not consist of single-surface amplitudes in only one, the horizontal, plane. Instead waves of vibration on the vocal folds can be distinguished in all three dimensions of space forming perpetually changing surfaces of very irregular configuration as can be seen for instance from Schönhärl's Fig. 16. This of course will affect the resulting echoes, as is illustrated in Fig. 8.

Certain difficulties may arise in the clinical application of the method. The cranio-caudal movements of the entire larynx during change of phonatory pitch (e.g. Kitzing & Sonesson 1967) and during deglutition may cause a momentary loss of the echo. Furthermore, the position of the transducer in relation to the vocal folds can be difficult to reproduce from one examination to another.

However similar problems were encountered and solved in echocardiography when recording mitral valve motion. As shown by Edler (1961) examination with TM-display can be standardized in such a way that clinically important information is obtained in spite of these difficulties. The reason for this is that, unlike surrounding structures, the structure under investigation, i.e. the mitral valve, is in constant motion which gives rise to characteristic and identifiable curves in TM-display. Conditions are analogous in the larynx.

ACKNOWLEDGMENTS

We are greatly indebted to Professor H. Hertz, Head of the Department of Electrical Measurements, Lund Institute of Technology and Ass. Professor B. Sonesson, Department of Anatomy, University of Lund, for placing technical and anatomical facilities at our disposal.

ZUSAMMENFASSUNG

Ausser der elektronischen Laryngostroboskopie, die wie bekannt von der subjektiven Auffassung des Untersuchers abhängt, gibt es keine allgemein angewandte Methode zur kontinuierlichen Registrierung von Stimmbandschwingungen. Es ist deshalb schwer für den Laryngologen bzw. Phoniater den Schwingungsvorgang an den Stimmlippen objektiv zu erfassen. Die vorliegende Arbeit befasst sich mit einer Methode für das Studium der Stimmbandschwingungen mit pulsierendem Ultraschall, der sog. Echoglottografie, die viele wesentliche Voraussetzungen aufweist, um die genannte Lücke in der Diagnostik der Stimmlippenfunktion zu schliessen.

Für die objektive, kontinuierliche Erfassung von Stimmlippenschwingungen wurde ein besonderes, hochempfindliches Ultraschallreflektoskop konstruiert, das die Verwendung von Schallköpfen mit verschiedener Ultraschallfrequenz erlaubt. Die Repetitionsfrequenz für die Ultraschallpulse betrug 10 kHz, womit bei genügender Eindringungstiefe des Ultraschalles im Gewebe eine vollkommen ununterbrochene Aufzeichnung des schnellen Schwingungsverlaufes gewährleistet werden konnte. In vorbereitenden Versuchen erwies es sich als möglich, sogar verknöcherten Knorpel noch bei Frequenzen bis zu

4 MHz ultraschallmässig durchzudringen. Diese Frequenz gestattet eine gute Auflösung bei der Aufzeichnung von sowohl Entfernungs- als auch Grössenschwankungen eines Objekts.

Als Ausgangspunkt für die weitere Entwicklung einer echoglottografischen Methode sind mit Ultraschall gewonnene Aufzeichnungen von menschlichen Kehlkopfpreparaten studiert worden. Hierbei wurden Aufnahmen der freien Stimmbandkante erzielt, deren Ursprung unzweideutig feststand. Beim Anblasen und Schwingen der Stimmbänder ergaben sich Aufzeichnungen von charakteristischen Kurven, deren Form im Prinzip mit Glottogrammen von anderen, umständlicheren Methoden übereinstimmte.

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QUANTITATIVE MEASUREMENT OF DROOLING

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Abstract A method for quantitative measurement of
drooling, utilizing the radioactive isotope ^{99m}techne-
tium, is introduced. The aim of this method is to
evaluate results of therapy against this state. Drool
ing patients were given 100 µCi ^{99m}Tc intravenously
Saliva samples were repeatedly taken from the mouth
for 9 hours and the isotope concentration was ex
amined. The drooled saliva was collected in dispos
able bibs. From the measured radioactivity in the bibs
and the saliva samples, the amount of drooled saliva
could be calculated. The results show as regards
saliva production in a normal population, great
variations in amount of drooled saliva within as well
as between individuals. With due precautions, the
method is useful for quantitative measurement of
drooling.

Every year between 200–300 children with
cerebral palsy are born in Sweden Among
these about 10 (Enfors & Lundberg 1968)
ill have an embarrassing drooling. This causes
much trouble to the child as well as to its par
ents or nursing personnel. Treatment against
drooling has hitherto mainly been medical
(Goode & Smith, 1970) A few cases surgically
treated are described in the literature (Wilkie
1967 Enfors & Lundberg 1968 Laage Hell-
man, 1969) The appraisal of the results after
treatment has hitherto only been subjective,
which makes a satisfactory comparison be-
tween different therapeutical results difficult.
A method for quantitative measurement of the
amount of drooled saliva therefore is desirable.
As the amount of drooled saliva generally does
not exceed 20 ml per hour evaporation is suf
ficiently important to preclude a simple weigh-
ing performance A method which utilizes the
radioactive isotope technetium (^{99m}Tc) is de-
scribed in this study

^{99m}Tc in the form of pertechnetate has in
recent years been increasingly used in different
studies of the function of the salivary glands
(Abramson et al., 1969 Gates, 1970 Harden
et al., 1969) Technetium was discovered in
1937 by Segré and was used clinically for
the first time by McAfee et al., who in 1964
made the first brain scan Technetium is found
in the group VII a of the periodic system to-
gether with manganese and rhenium. The
reason why technetium is so suitable for me-
dical investigation is its physical properties.
^{99m}Tc is a daughter nuclide of molybdenum
(^{99}Mo) has a physical half life of 6 hours and
is a gamma-emitter of 140 keV The deposi-
tion in the body is extremely small. The com-
pound most frequently used is the peroxyanion
TcO_4^- also called pertechnetate. This ion is
fairly stable, resembling iodide in its distribu-
tion in the human body Both ions are con-
centrated in the salivary glands, iodide about
40 times and pertechnetate about 20 times the
plasma values (Harden & Alexander 1967
Gates, 1970. One hour after intravenous in-
jection of pertechnetate, 30% of the activity is
found in the red cell fraction and 70% in th.
plasma. 75% of the plasma activity is protein
bound (McAfee et al., 1964).

The radioactive daughter ^{99}Tc arises from
decay of ^{99m}Tc. The radiation dosage of ^{99}Tc

This study was supported by Grants from Folke Ber
nadotte Stiftelsen and First of May Flower Annual
Campaign for Children's Health

is negligible, because of a very long physical half-life (2×10^5 years). Excretion of ^{99m}Tc is quickest within the first 24 hours after administration, and mainly in the urine (Harper et al., 1965).

One advantage of pertechnetate compared with iodide is that the activity used for scintigraphy results in less radiation dose to the investigated person. A thyroid scintigram with the usual activity of 50 μCi J^{131} results in an irradiation against the gland of about 100 rad. If ^{99m}Tc is used instead, in the ordinary dose of 1 mCi, the thyroid gland is irradiated 1 000 times less, i.e. 100 mrad (Harper et al. 1965). To prepare a salivary gland scintigram, a sufficient dose would be 100–200 μCi ^{99m}Tc, i.e. an irradiation in the salivary glands of 4–8 mrad (Grünberg & Börner 1966).

Within 15 minutes of intravenous administration of pertechnetate, the isotope is found in the saliva. The most likely site for the concentration of the isotope is the ductal epithelium (Abramson et al., 1969) After intravenous injection of pertechnetate, the isotope could be demonstrated in the great, paired, salivary glands as well as in the acinar glands in the oral mucosa. It has long been well known what happens to iodide in the body after intravenous or peroral administration. Experiments with pertechnetate indicate the same distribution. Harden & Alexander (1967) compared the clearance of iodide and pertechnetate in the parotid gland. They found that increased secretion of saliva resulted in higher clearance of both iodide and pertechnetate, the relation, however being constant 2 1 An increased secretion rate resulted in lower viscosity and lower concentration of technetium in the saliva. Harden considers that pertechnetate and iodide share a common transport mechanism.

The aim of the present investigations was to measure the amount of drooled saliva. First of all, the best suited conditions for the investigation had to be determined. The criterion was that the absolute change of concentration had to be small within the actual time interval. In the first series, changes in salivary concentration of the isotope after intravenous injection were studied. From these results a second series was planned where the amount of drooled saliva was determined by measuring the radioactivity of the bibs where drooled saliva was collected and of saliva samples taken during the same period.

MATERIAL AND METHOD

Series No I

The series comprised 14 persons with brain damage mainly in the form of cerebral palsy The age distribution was 9–23 years, 8 women and 6 men. Every patient was investigated twice After intravenous injection of 100 μCi ^{99m}Tc, saliva was taken from the frontal part of the mouth every 15 min during the first hour and then after 1.5 2, 3 and 4 hours. The samples were placed in airtight plastic cylinders which were examined in respect of radioactivity The measuring device was a scintillation spectrometer type Picker Autowell with a 3-inch well crystal of sodium iodide. From the injected isotope solution a sample was withdrawn as a reference before the start of the investigation. The reference solution was used to show the decay of the isotope The reference solution and the saliva samples were measured in identical geometry The relation between radioactivity in saliva samples at different times and the reference solution was expressed in % of a given amount of radioisotope per gram of saliva. The mean figures from this series are shown in Table I Since the amount of radioisotope given was 100 μCi, the salivary isotope concentration in g of saliva corresponds to the same figures expressed as μCi g.

Discussion

The aim of this series of investigations was first to find out how the salivary concentration of ^{99m}Tc varied after intravenous administration. From the natural relation to the plasma concentration curve, one might expect that the isotope concentration in saliva would have a quick initial decrease followed by a slower secondary phase, which is mostly the result of a continuous excretion The second purpose of this survey was to estimate the time interval suitable for the quantitative measurement of the amount of drooled saliva. In order to find an interval with a low relative variation, the observed mean values were compared to a model of regression representing

a constant, relative reduction of the salivary isotope concentration.

The mathematical model used is then assumed to be

$$Y = a\, e^{-bt} \quad t>0 \quad a>0 \quad b>0$$

where Y represents the mean of salivary concentration of ⁹⁹ᵐTc and t the time after injection a and b are unknown constants and e is the base of natural logarithms. The mathematical model was fitted to the values in Table I

The results are shown in Fig 1 The fit of the mathematical model is not good in the first period. The relative reduction in salivary isotope concentration expressed in % per gram of saliva is greater at the beginning than at the end of the period of investigation With these results as a background it is evident that quantitative measuring of drooled saliva should not start until 120 min after intravenous injection of ⁹⁹ᵐTc. One more reason for choosing this period is the greater individual variations of the concentration values seen at the beginning of the investigation The series also shows that the process can be regarded as approximately linear from this point of time which simplifies the calculations made in series no 2. The effects of the change caused by the continuous excretion of the isotope is, however due to the prolonged observation period, still as great, and must be borne in mind in the evaluation of the results.

Table I *Observed values of ⁹⁹ᵐTc-concentration in saliva*

14 patients investigated twice (224 samples). Given dose 100 μCi

Time after injection (minutes)	Concentration (%/g or μCi/g)		
	Max.	Min.	Mean
15	0.91	0.17	0.35
30	0.54	0.15	0.29
45	0.67	0.10	0.26
60	0.52	0.08	0.23
90	0.51	0.09	0.20
120	0.33	0.10	0.18
180	0.28	0.08	0.15
240	0.27	0.07	0.12

Series No 2

Quantitative measurement of drooling was made in 12 persons with brain damage mainly in the form of cerebral palsy Their intellect varied from normal to idiocy The age distribution was 6–26 years in 11 persons and the last one was 46 years old. There was an equal distribution between the sexes. The investigations were made mainly in the institution where the patients lived in order to minimize changes in the daily routine and environment.

Discussion

Based on the results from series no. 1 the measurements were made 120–540 min after intravenous injection of 100 μCi of ⁹⁹ᵐTc. The drooled saliva was collected in disposable bibs 40 × 50 cm made of one layer of a plastic sheet between two layers of cellulose wadding (Mölnlycke art. 720500)

Each bib was placed around the patient's neck for half an hour and was afterwards put into a plastic bag, which was then measured in respect of radioactivity The measuring device consisted of a Packard Model 3002 Tri-Carb scintillation spectrometer and an Armac Model 440 scintillation detector Each time the bib was changed a sample of saliva was taken with a pipette from the frontal part of the mouth. The saliva was put into an airtight plastic cylinder and weighed whereafter the radioactivity was determined in a spectrometer type Picker Autowell with a 3-inch well crystal of sodium iodide. A reference solution was used to show the decay of the isotope. Identical measuring geometry between the reference solutions and the saliva samples as well as the bibs was arranged. The measured radioactivity per weight unit of saliva and of the bibs, was used to calculate the amount of drooled saliva.

RESULT

The calculated figures of drooled saliva in g per 30 min received from the 12 patients in series no 2 are shown in Table II Each value is the mean of 14 measurements. Altogether 42 measurements of drooled saliva were made on every patient. Within one individual there could be a variation of 0.4–4 0 g drooled saliva

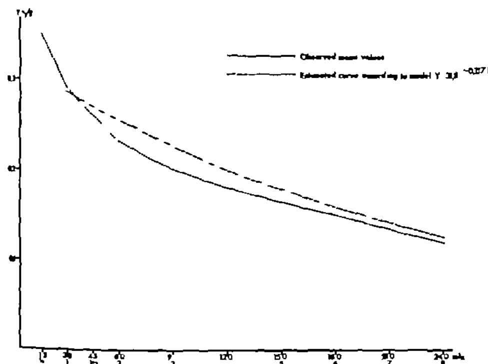


Fig. 1. Salivary concentration of ^{99m}Tc.

per 30 min. These variations existed independently of the investigations being made within a few hours or several weeks. Variations between individuals were found from 0.4–16.7 g drooled saliva per 30 min.

STATISTICAL ANALYSIS

1. *Analysis of regression*

On three different occasions 14 measurements were made. To reduce the errors of the method in analysing the results, the average salivary isotope concentration values at different times, could be calculated for each person from the equation of linear regression, which, based on the results of series no. 1 could be accepted. The model of the equation this time was $Y = a + b \cdot t$. The concentration values were then used for the calculation of drooled saliva, thereby reducing the errors by 10–20%.

2. *Analysis of variance*

The values of drooled saliva in g per 30 min were treated with analysis of variance to test the variations between the individuals and the variations between the means for different investigations of the same individuals. Statistically significant differences were received for both sources of variation. The results are shown in Table III.

DISCUSSION

The present paper describes a method for the quantitative measurement of drooling by using the radioactive isotope ^{99m}Tc. The aim was to make it possible to evaluate results of therapy against drooling. In evaluating the method some errors ought to be discussed. (*a*) variations in salivary isotope concentration, (*b*) variations in amount of saliva produced, (*c*) variations in amount of drooled saliva, (*d*) risk of irradiation.

In an article from 1967 Harden shows that the salivary concentration of ^{99m}Tc diminishes when the velocity of secretion is higher. This means that if the saliva sample is taken during a phase with high secretion rate, the

of drooled saliva is overestimated. The opposite result is obtained if the sample is taken in a phase of low salivary secretion. Hence this error is randomized.

It is well known from the literature that there are great variations of saliva production in human beings (Becks & Wainwright, 1943 Gerke & Klemt, 1951 Schneyer 1956 Rauch 1959 Enfors, 1962) This fact is true both within the same person at varying times and between different persons. Even if it is not clear whether a drooling person drools a constant fraction of the total saliva produced it is possible that the great variations in amount of drooled saliva described are mainly explained by the variations in the total amount of saliva produced. From a methodological point of view these variations are embarrassing. We therefore have tried in this investigation to avoid factors influencing the total amount of saliva production. For this reason the measurements are made in the environment where the children live, trying to maintain as far as possible the daily routine including the regular meals, and with the ordinary nursing personnel present. The actual situation of investigation however must influence the saliva production too With the knowledge of these variations it is evident that this measurement of drooling must be performed over a relatively long period and must be based on many samples. How great a number of samples, depends on the accuracy demanded in calculating the mean.

At the time of investigation the patient receives 100 μCi ⁹⁹ᵐTc intravenously which gives an irradiation in the salivary glands of about 4 mrad (Grünberg & Börner 1966) The calculated dose in the gonads in such a patient will be 1.2–1.6 mrad (Smith, 1965) As a comparison a conventional X-ray examination of the hypopharynx and oesophagus gives an irradiation of the gonads of about 20 mrad (Hammer Jacobsen, 1963) Thus the dose to the examined person in quantitative measuring of drooling is small.

Even if great changes of drooling in individuals with cerebral palsy can be observed by the nursing personnel, subjective observations of this kind cannot possibly be used to evaluate the results from different kinds of therapy given to a group of patients. The basis for correct evaluations must be a more objective method. If proper consideration is given to the above analysed errors and if a sufficient number of measurements are made, the method described in this paper is useful for quantitative measurements of drooled saliva.

Table II *Mean values of drooled saliva (g/30 min)*

Each value is the mean of 14 measurements (504 samples)

Patients	Time of investigation I	II	III
K. A.	9.22	4.27	1.87
C. H.	3.16	2.52	3.08
B. J	8.52	11 78	9 41
P J	2.07	3 49	3.62
B. K.	8.59	8.62	7.87
A. L.	6.12	1 79	3.86
B. O	5 43	6.01	5 08
C. P	1.59	1 17	2.60
J P	2.06	8.52	2.49
M. S.	5.01	2.95	3.33
L. S.	4 02	5 74	1.83
L. U	7 11	8.45	11.53

Table III *Analysis of variance on drooled saliva values (g/30 min)*

Sources of variations	Degrees of freedom	Mean squares	F	Coefficient of variation (%)
Between individuals	11	271 86	5.28	44
Within individuals				
Different times of investigation	26	31 43	6.59	34
Same time of investigation	468	7 80		54

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ZUSAMMENFASSUNG

Eine Methode für die quantitative Messung von geifrigem Speichel wird vorgelegt. Die Methode benutzt den radioaktiven Isotop ^{99m}Technetium und soll die Resultate der Therapie gegen Geifer schätzen. Geifernde Patienten bekamen 100 μCi ^{99m}Tc intravenös. Speichelproben wurden während 9 Stunden wiederholt dem Mund entnommen, worauf die Konzentration des Isotops gemessen wurde. Der geifrige Speichel wurde in einem Geiferlatz gesammelt. Aus der gemessenen Radioaktivität des Geiferlatzes und der Speichelprobe konnte die Menge geifrigen Speichels berechnet werden. Die Resultate zeigen, in Übereinstimmung mit dem Speichelsekret einer normalen Population, grosse Unterschiede der Menge geifrigen Speichels sowohl bei einer als auch unter den untersuchten Personen. Eine Variationsanalyse wird gemacht, und die Fehler werden diskutiert. Insgesamt ist die Methode brauchbar geifrigen Speichel quantitativ zu messen.

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ADAPTATION OF HORIZONTAL SEMICIRCULAR CANAL RESPONSES

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Abstract. The torsion pendulum model predicts semicircular canal responses when angular accelerative stimuli are relatively brief, but certain discrepancies appear when accelerations are sustained for a longer time. A recently proposed revision of the torsion pendulum model accounts for many of these discrepancies on the basis of a short-term adaptation process. The revised model was tested by comparing its predictions with the observed responses of subjects exposed to a series of prolonged accelerations. The model described these data fairly accurately although minor discrepancies remained, suggesting the existence of additional adaptation processes. A new method is described for measuring the adaptation process described by the model. This method is based on a single measurement that can be obtained with relative ease for either nystagmus or sensation responses.

A mathematical model can be of considerable value in the study of a sensory system. A model provides a general equation from which the responses can be predicted for any stimulus within a specified range Further if the model is parsimonious and the system under consideration is reasonably simple the response can be completely specified by a small number of parameters.

The torsion pendulum model of the semicircular canal system (Van Egmond et al., 1949) is such a model. It permits specification of the response to any angular accelerative stimulus if the values of two parameters—the cupula long time constant (τ) and the response gain (K^{*}_{λ})—are known The value of this model is widely recognized but its range of application is limited by the fact that it accurately describes responses only when the semicircular canal stimulus is relatively brief Whenever an acceleration is prolonged beyond a few seconds, the observed response departs systematically from the model's prediction (Mowrer 1935 Ek et al., 1960 Guedry & Lauver 1961) A number of workers (Ek et al., 1960 Hood, 1961 Aschan & Bergstedt, 1965 Guedry 1965) have suggested that this discrepancy is not caused by an error in the model itself but rather by the intervention of response adaptation, for which the model does not account.

A more comprehensive model, which includes both the torsion pendulum model and an adaptation term has been proposed by Young & Oman (1969) and by Malcolm & Jones (1970) These authors assume that the observed semicircular canal response is proportional to the difference between the input signal from the canals and a "zero-velocity reference level," which exists somewhere within the nervous system. The response appears to adapt because this reference level shifts during sustained stimulation in the direction that reduces the difference between itself and the sensory input level. The authors further assume that the rate at which the reference level shifts is dependent upon the magnitude of this difference.

The revised model, if correct, considerably extends the range of accurate prediction. It has already proven successful in predicting responses to several types of prolonged accelerations (Young & Oman, 1969). The mode also parsimonious. In addition to the

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rameters (τ_C and $K_{\overline{\lambda}}^{\phi}$) mentioned previously the model includes only one other parameter—an adaptation time constant (τ)

Methods have been previously described for estimating the τ and $K_{\overline{\lambda}}^{\phi}$ parameters (Guedry et al. 1971 *a* *b* Gilson et al. 1973) which meet practical requirements with respect to subject comfort and administration time. These methods are of course based on the use of brief stimuli in which the confounding effects of adaptation presumably do not occur In this investigation an attempt is made to develop a method of estimating the adaptation parameter (τ) that also meets practical requirements for routine use.

This report describes two experiments. The first examines the ability of the revised model to describe responses to the particular type of stimulus under consideration and thus provides an additional test of the model s validity The subjects in this experiment are tested under two conditions of mental alertness to determine if the level of alertness has any influence on the rate of adaptation The second experiment evaluates a proposed method for estimating τ_a.

EXPERIMENT 1

rocedure

ẟ U.S Navy flight students served as subjects. All had passed U.S Naval flight physical examinations without evidence of vestibular disorder Each student was administered four semicircular canal stimuli with the horizontal canals in the plane of rotation. The stimulus in each case was an angular acceleration of 5 deg/sec² for 60 sec, followed immediately by a deceleration of the same magnitude and duration Nystagmus was recorded during, and for 3 min after each presentation of the stimulus by the electrooculographic method. During two of the trials (one clockwise and the other counterclockwise) the subject was kept alert with mental arithmetic. During the other two trials (one clockwise and the other counterclockwise) he was unoccupied by any task and was told to relax. The order of administration of trials was counterbalanced across subjects to avoid contamination of the results by serial effects.

Since it is known that dark adaptation affects the corneoretinal potential (Gonsbor & Malcolm 1971) all subjects were completely dark-adapted before the experiment began and were maintained in red light during the 10 min rest periods between trials. Subjects were always in complete darkness while nystagmus was being recorded.

Results and discussion

The data shown in Fig. 1 represent the averaged nystagmus responses of all six subjects while they performed mental arithmetic. The responses of these subjects clearly show the phenomena attributable to adaptation viz., a response decline during constant acceleration, and a secondary response appearing after the stimulus had ceased. The torsion pendulum model predicts neither of these phenomena, but as shown in Fig 1 the revised model provides a reasonably accurate description of both. Parametric values were selected by first setting τ at 16 sec, a value that has been found previously (Gilson et al., 1973), then choosing values of $K_{\overline{\lambda}}^{\phi}$ and τ to obtain the best visual fit to the data. The optimum value of τ was 120 sec, which is similar to the values found by other investigators to provide the best fit with data from a variety of sources (Young & Oman 1969 Malcolm & Jones, 1970).

To the extent that the data match the theoretical curve, they confirm the adequacy of the revised model. The fit of the model is acceptable, although minor discrepancies exist, which may suggest the operation of other adaptation processes besides the one described by the model. One such process might be a progressive reduction of the response gain ($K_{\overline{\lambda}}^{\phi}$) during sustained acceleration. A preliminary effort at describing the data with a model that includes a progressive gain reduction has yielded a better fit than does the

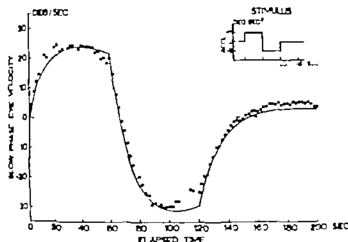


Fig 1 Nystagmus response to a triangular waveform stimulus when subjects were alert (●). Data for clockwise and counterclockwise rotation are combined positive values indicate nystagmus slow phase velocity opposite the direction of rotation (6 subjects × 2 trials). Also shown is the revised model's prediction of the response with τ = 16 sec and τ = 120 sec. The response obtained while subjects were not alert is not shown an accurate fit to those data was obtained by decreasing the value of K_3^{ϕ} without altering the values of τ or τ_a.

prediction shown in Fig 1 However the improvement is rather slight for the stimulus used here. Experiments are underway using more prolonged stimuli that are designed to clearly demonstrate a progressive gain reduction, if in fact one exists.

During the trials in which subjects had no task to perform, the nystagmus responses were reduced, as expected from previous studies (Guedry & Lauver 1961 Collins & Guedry 1962). However this reduction (about 10%) was not as great as some investigators have found. It is quite possible that, since the subjects were student aviators undergoing a period of intense evaluation at the time of testing, they found the experimental situation too alerting and could not relax appreciably during the trials in which they had no task to perform. The small reduction that was found could be accounted for by substituting a lower response gain (K_3^{ϕ}) into the prediction equation while keeping the value of τ unchanged. Thus, the adaptation rate did not appear to be influenced by the level of alertness in this study but there remains a possibility that such an effect might have been revealed if greater differences in alertness had been obtained.

EXPERIMENT 2

It is well known that the sensation of rotation exhibits a faster decline during prolonged rotation than does nystagmus (Ek et al., 1960 Guedry & Lauver 1961) Young & Oman (1969) accounted for this phenomenon in their revised model by assuming that the adaptation rate is faster (i.e., τ is smaller) for sensations than it is for nystagmus. This assumption implies that adaptation occurs somewhat independently in these two response systems. If so, then any method for assessing adaptation should be applicable to both of them. Most investigators have preferred to observe nystagmus, methods that have been developed for measuring sensations are generally too laborious for routine use. However a recently reported technique for measuring subjective turning points (Guedry et al., 1971 *a*) appears suitable for this purpose. Under this method, the subject is exposed in darkness to a series of stimuli like those used in the previous experiment. The sensation of a normal individual in this situation is similar in form to the nystagmus response shown in Fig 1 i.e., he first experiences acceleration in the proper direction then deceleration, then a momentary pause, and then commencement of rotation in the opposite direction. The subject's task is to signal at the moment he experiences this reversal in direction of rotation.[1]

[1] After the stimulation stops, the subject will experience deceleration again, and, if the stimulus is sufficiently long, he may experience another reversal in the direction of rotation (see Fig. 1). This reversal was not studied in this experiment.

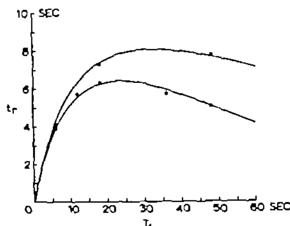


Fig. 2. t values for nystagmus (●) and for sensation (○) to stimuli of various durations (6 subjects × 6 trials). Also shown is a description by Eq. 1 of nystagmus data with $\tau = 16$ sec and $\tau = 150$ sec, and a description of sensation data with $\tau = 16$ sec and $\tau = 50$ sec.

If t is the time interval from the end of acceleration to the sensation of reversal, T_1 is the duration of acceleration τ is the time constant of the cupula response, and τ is the time constant of adaptation, then

$$t = \left(\frac{1}{1/\tau_a - 1/\tau_c}\right) \ln\left(\frac{2-e^{T/\tau}}{2-e^{T/\tau}}\right) \qquad \text{(Eq. 1)}$$

Thus, t depends upon the values of two parameters—τ and τ_a. When τ is known τ for sensation can be determined.

Eq. 1 can be used to determine τ for nystagmus as well, since nystagmus t can be easily found by measuring (on the nystagmus record) the time interval from the end of T_1 until the reversal in the direction of nystagmus.

In this experiment subjects were exposed to a series of prolonged stimuli and values for both sensation and *nystagmus* τ were determined.

Procedure

Six individuals (Naval officers and laboratory personnel) served as subjects in this experiment. All were free from obvious vestibular defects. Each subject was exposed in darkness to a series of triangular waveform stimuli in the plane of the horizontal semicircular canals. The stimulus in each case was an angular acceleration of 5 deg/sec for a given duration followed immediately by a deceleration of the same duration and magnitude. The duration of the acceleration phase of the stimulus (T_1) was varied in seven steps (T_1 = 6, 12, 18, 24, 36, 48, and 60 sec) with each duration presented six times (three times in the clockwise direction and three times in the counterclockwise direction in alternating order). The order of administration of stimuli was randomized across subjects to avoid serial effects. Rest periods equal to approximately five times the stimulus duration were allowed between trials, and the test series was spread over four testing sessions to minimize subject fatigue.

On each trial nystagmus was recorded, and subjects were asked to press a button at the moment they experienced the reversal in the direction of rotation. The t for sensation was determined for each trial by measuring the interval from the end of T_1 until the push-button response and t for nystagmus was determined by measuring the interval from the end of T_1 until nystagmus reversal. From these data, the values of subjective τ_a and nystagmus τ were estimated.

Results and discussion

Eq. 1 specifically predicts that, as T_1 increases, the t interval will grow longer until it reaches a maximum and then it will begin to grow shorter. Furthermore, if the subjective response does in fact adapt faster than nystagmus, the t for sensation should reach a maximum sooner than t for nystagmus and then decline more rapidly. The data, shown in Fig. 2, confirm all of these predictions. With τ set at 16 sec, an acceptable fit with the nystagmus data was obtained when τ for nystagmus was 150 sec, and a fit with subjective data was obtained when τ for sensation was 50 sec. Both values are somewhat similar to those employed by Young & Oman (1969) to describe data from other sources. The accuracy of the prediction thus offers additional support for the

revised model, including the assumption that the adaptation rate for the sensation of rotation is faster than the adaptation rate for nystagmus.

The method used here for measuring adaptation rate appears to yield reliable results suitable for routine assessment of individual differences, since it utilizes a single response measurement (t) that can be obtained relatively easily for either nystagmus or sensation. Most subjects are able to make consistent judgments of the subjective reversal with only brief instruction. However it was found that each subject must fully understand that he is to respond *immediately* after experiencing the reversal. Otherwise spuriously long t values were obtained.

In this experiment the testing procedure was somewhat lengthy because the subjects were exposed to seven durations of stimulus in order to provide enough data for an adequate test of the model. In practice, of course, only one stimulus duration (for example, $T_1 = 60$ sec) need be presented to obtain an estimate of τ_a, and the number of trials can be chosen to meet practical requirements. The method requires separate determination of the cupula time constant (τ_c), but this value can be estimated by methods described in a previous report (Gilson et al. 1973).

An accurate description of the adaptation process significantly expands the universe of prediction, permitting prediction of responses under circumstances in which adaptation occurs or on the other hand, permitting selection of vestibular testing situations that avoid the confounding effects of adaptation. The diagnostic significance of adaptation measurements in detecting vestibular disorders remains to be determined by evaluation with clinical case material, but for some applications, such as evaluation of flight personnel, assessment of adaptive ability has a certain face validity since aviators must frequently cope with prolonged accelerations during aircraft maneuvers.

There is no assurance that the process described by this model fully accounts for all adaptation phenomena in fact, there are clear indications to the contrary (Guedry 1972) and the data obtained in this experiment suggested the possibility of additional processes. Nevertheless, the revised model represents a substantial improvement over the original torsion pendulum model in the prediction of responses to prolonged angular accelerations, and thus provides a rational basis for selection of adaptation measurements.

This report is based on work completed at the Naval Aerospace Medical Research Laboratory while the first and second authors were on active military duty in the U.S Army and Navy respectively

Opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the view or the endorsement of the Departments of the Army or Navy

ZUSAMMENFASSUNG

Für Winkelbeschleunigungsreize von verhältnismässig kurzer Dauer werden die Reaktionen der Bogengänge vom Torsionspendelmodell vorausgesagt. Bei längerer Dauer der Beschleunigungen treten jedoch gewisse Abweichungen auf. In einer neuerdings vorgeschlagenen, verbesserten Form des Torsionspendelmodells werden viele dieser Abweichungen mit einem kurzfristigen Anpassungsprozess erklärt. Zur Prüfung des umgearbeiteten Modells wurden dessen Voraussagen mit den tatsächlich beobachteten Reaktionen bei Versuchspersonen verglichen, die einer Reihe von langandauernden Beschleunigungen ausgesetzt worden waren. Das Modell beschrieb diese Ergebnisse ziemlich genau, obwohl unbedeutende Abweichungen bestehen blieben, was auf zusätzliche Anpassungsprozesse hinweist.

Eine neue Methode zur Messung des vom Modell beschriebenen Anpassungsprozesses wird dargelegt. Diese Methode beruht auf einer Einzelmessung, die verhältnismässig leicht entweder für Nystagmus oder für Empfindungsreaktionen durchgeführt werden kann.

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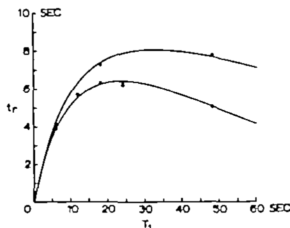


Fig 2 t values for nystagmus (●) and for sensation (○) to stimuli of various durations (6 subjects × 6 trials). Also shown is a description by Eq 1 of nystagmus data with $\tau = 16$ sec and $\tau = 150$ sec, and a description of sensation data with $\tau = 16$ sec and $\tau = 50$ sec

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On each trial nystagmus was recorded, and subjects were asked to press a button at the moment they experienced the reversal in the direction of rotation The t for sensation was determined for each trial by measuring the interval from the end of T_1 until the push-button response and t for nystagmus was determined by measuring the interval from the end of T_1 until nystagmus reversal. From these data the values of subjective τ and nystagmus τ were estimated.

Results and discussion

Eq 1 specifically predicts that, as T_1 increases, the t interval will grow longer until it reaches a maximum and then it will begin to grow shorter Furthermore if the subjective response does in fact adapt faster than nystagmus, the t for sensation should reach a maximum sooner than t for nystagmus and then decline more rapidly The data, shown in Fig. 2, confirm all of these predictions. With τ set at 16 sec, an acceptable fit with the nystagmus data was obtained when τ for nystagmus was 150 sec, and a fit with subjective data was obtained when τ for sensation was 50 sec. Both values are somewhat similar to those employed by Young & Oman (1969) to describe data from other sources. The accuracy of the prediction thus offers additional support for the

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THE INFLUENCE OF DRUGS ON CALORIC INDUCED NYSTAGMUS

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Abstract. The influence of both the activating and the inhibitory power of voluntary fixation upon caloric nystagmus has been studied. Eight normal test subjects were given bithermal caloric irrigations to evaluate the influence of fixation and no fixation under various test conditions. The following effects were observed:

(1) Eye closure (i.e. with no fixation) has a facilitating power on the nystagmus in normal persons but inhibits or abolishes the induced nystagmus under the influence of reticular formation-blocking drugs.

(2) Eye opening (with fixation) diminishes or abolishes the nystagmus induced in normal persons, and increases or revives the nystagmus in persons given the reticular formation blocking drugs

(3) It is concluded that, when the caloric test is performed, the resultant nystagmus should be examined under each of the two conditions of eye closure (no fixation) and eyes open (fixation) This may add useful diagnostic information to the oto-neurological evaluation of patients. Electronystagmographic examination conducted only with the eyes closed may provide misleading information concerning vestibulo-oculomotor function.

The concept that the vestibulo-ocular reflex arc has more than one neuronal pathway has been accepted for a number of years (Lorente de Nó 1933 1938 Spiegel & Price, 1939 Szentágothai, 1950· Szentágothai & Schäb 1956· Bender 1955 McCabe 1965). The medial longitudinal fasciculus has been accepted as the basic neuronal structure of the elementary three-neuron vestibulo-ocular mechanism Its role, however is apparent only in contractive responses (Lorente de Nó, 1933 Szentágothai, 1950· Szentágothai & Schäb, 1956) The second pathway as was first shown by Lorente de Nó (1933, 1938) consists of internuncial chains within the reticular formation

The specific effect of certain drugs on the reticular formation has been reported by several authors (Moruzzi & Magoun, 1949· Bradley & Elkes, 1957 McCabe 1965 Alema et al. 1966). Its influence on the quick component of vestibular nystagmus has been demonstrated by Bender (1955) Bender et al. (1955) Anderson et al. (1958) Nathanson & Bergman (1958), Jongkees & Philipszoon (1960), Jatho (1965) McCabe (1965). There exist drugs which act directly on the reticular formation, either by a depressant action such as the barbiturates (Moruzzi & Magoun, 1949· Bradley & Elkes, 1957 Killam & Killam 1958) and alcohol, or by an excitant action, e.g. amphetamine (Bradley & Elkes, 1957) The barbiturates are believed by some authors (Moruzzi & Magoun, 1949· Bradley & Elkes, 1957) to block the conduction in the medial pathways at the brain stem level. Unconsciousness, sleep and the upper level of anesthesia block the quick component of nystagmus, the eyes move to the side of the slow component, and the induced nystagmus is never completed (McIntyre, 1939 Nathanson & Bergman, 1958 Blegvad, 1962)

In recent years, the ocular influence upon vestibular nystagmus has attracted many

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searchers. Clinical experience of routine caloric testing of the vestibular organ has shown that, with fixation of gaze, there is a suppression of nystagmus, both with respect to the speed of the slow component and the duration (Aschan et al. 1956 Henriksson, 1956 Mahoney et al. 1957). There are cases in which nystagmus may be abolished completely by fixation. When the eyes are closed and fixation is abolished, the nystagmus will appear enhanced in all its features (Collins, 1962, 1968 Jongkees & Phillipszoon, 1964 Sokolovski, 1963 1966)

However the existence of a nystagmus which is primarily and possibly only seen on fixation and its disappearance under the conditions which diminish fixation has been known since Holmes publication on acute cerebellar injuries in 1917 (Holmes, 1917 Rashbass & Russell, 1961 Naito et al. 1963 Dix & Hallpike 1966 Hart, 1967). Thus, the problem of the enhancing or abolishing power of ocular fixation on nystagmus appears to be still unsolved.

In an attempt to throw more light upon this phenomenon, the present investigation was carried out. Using normal subjects, we examined the influence of voluntary fixation upon nced vestibular nystagmus and the influence drugs that are believed to act on the brain reticular formation.

METHOD

Subjects

Eight young subjects, who were all university graduates or students, were employed for this study None had a history of ear trouble or vertigo. All were examined audiometrically to establish that their hearing was normal. All eight had otoscopically normal ear canals and tympanic membranes.

Examination of equilibrium and for both spontaneous and positional nystagmus were performed on each subject and found to be normal.

Apparatus

The thermal stimulus was provided by a thermostatically controlled water bath to provide temperatures of 44 C and 30 C at the end of the tube The electronystagmograph recording apparatus was the Elema direct writing mingograph, M34 A time constant of 5 sec and a paper speed of 10 mm per sec were used. Surface electrodes were placed at each outer canthus of the subject s eyes to record the horizontal component of eye movements. A ground electrode was taped to the forehead. The whole unit was calibrated by asking the subject to follow two flashing lights 10 apart on the ceiling. The calibration was repeated after each irrigation The sensitivity of the recording apparatus was adjusted to give a pen deflection of about 1 mm per 1 eye movement

Procedure

The bithermal caloric test advocated by Fitzgerald & Hallpike (1942) was employed. The period of irrigation lasted 40 sec. The subjects were tested in a semi-dark room and, in addition, throughout all tests, a serial seven subtraction task was performed. Initially the induced nystagmus was recorded with the eyes closed (i.e. without fixation). After a period of 80 sec (from the onset of irrigation) the subject was instructed to open his eyes and look for a period of 20 sec at an illuminated point on the ceiling. The point was in the direct line of gaze and at a distance of 1.27 meters from the subject s eyes. After this 20 sec period, the subject was again instructed to close the eyes and the nystagmus was recorded until it disappeared. Following each caloric test optomotor nystagmus was recorded.

The eight normal subjects were submitted to caloric stimulation under five different test conditions. An interval of 7 days separated each test The order of the tests was as follows: (1) Control test. (2) After administration of alcohol. 100 mg of gin was given orally 30

min prior to the test (3) After administration of barbiturate: 200 mg of sodium amylobarbitone was ingested 1 hour prior to the test. (4) After administration of amphetamine. 5 mg of *d*-amphetamine was administered orally 30 min prior to the examination (5) Final control test.

Analysis

Only the data on responses following irrigations of the right ear with water at 44 C were analysed. An analysis was made of each nystagmic reaction with eyes closed (i.e without fixation) and with the eyes open (i.e. with fixation) during the culmination period of the caloric reaction. Two indices of response were used: (1) Stahle's (1956) measure of maximum velocity and (2) frequency of the induced nystagmus. The velocity measure was calculated by taking the mean eye speed during a 10 sec period at the peak of the response (Stahle 1956, 1958). The frequency was obtained by counting the number of beats over a 10 sec period at the culmination of the reaction (Torok, 1967 Hinchcliffe: 1968)

RESULT

The mean values were calculated for each of the two indices and under the different test conditions (Figs. 1 and 2)

In the control tests (drugs not administered) the velocity measure of the induced nystagmus with eyes closed (i.e. without fixation) was markedly increased in comparison with the nystagmus recorded with the eyes open (i.e. with fixation). The introduction of active visual fixation resulted in significant reduction in the velocity and frequency measures (Figs. 3 1 and 2).

Alcohol ingestion

The results of the test with alcohol (Fig. 4) showed very irregular caloric-induced nystagmus during eye-closure as compared with that with the eyes open (i.e. fixating) The mean velocity and frequency values, however

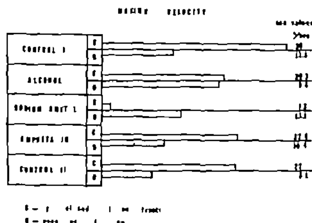


Fig 1 Mean values of maximum velocity (expressed in degrees per second) of postcaloric nystagmus during eye closure (no fixation) and eye opening (fixation) for temperature 44°C, right ear different test condition

are almost equal during eyes open and eyes closed (Figs. 1 and 2)

Barbiturate ingestion

Following ingestion of barbiturates, the nystagmus recorded with eyes closed failed to appear at all in many instances, or if present, was irregular and the beats weak (Figs. 5 and 6). With the eyes open and fixating, one can see well developed, regular nystagmus. However the velocity measure of the nystagmus

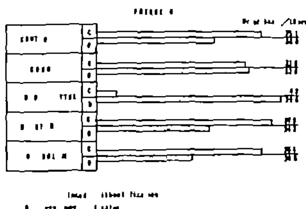


Fig 2 Mean values of frequency (expressed in mean number of beats per 10 seconds) of postcaloric nystagmus during eye closure (no fixation) and eye opening (fixation) for temperature 44°C, right ear different test condition.

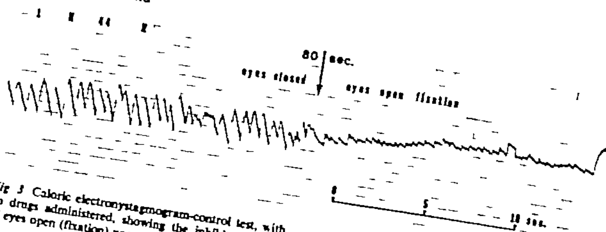


Fig 3 Caloric electronystagmogram-control test, with no drugs administered, showing the inhibitory effect of eyes open (fixation) upon the induced nystagmus.

during fixation was not essentially different from that of the induced nystagmus during fixation in subjects where barbiturates were not administered (Fig. 1) the frequency measure was much higher

Amphetamine ingestion

Here the nystagmus observed with the eyes closed is greater than that observed with the eyes open (Figs. 7 1 and 2) The effect of amphetamine was to improve the regularity of both the frequency and the amplitude of nystagmus during eye closure With the eyes open no difference was observed in either the velocity or the frequency measures of the induced nystagmus as compared with the control tests.

The average values for the two measures of nystagmic response for the five conditions are shown graphically in Figs. 8 and 9 An analysis of variance for the results obtained under the five test conditions showed that, for both velocity and frequency measures of the induced nystagmus responses where drugs had been given were significantly different from the control responses ($p > 0\ 001$).

DISCUSSION

These experiments have shown that, under the influence of sodium amylobarbitone, which is believed to block the reticular formation, caloric stimulation does not induce any consistent wave forms of nystagmus when examination was performed with eyes closed (i.e. no fixation) However with the eyes open and attempted fixation the appearance of vestibular nystagmus, which was not previously apparent was striking (Figs. 1 2, 5 6, 8

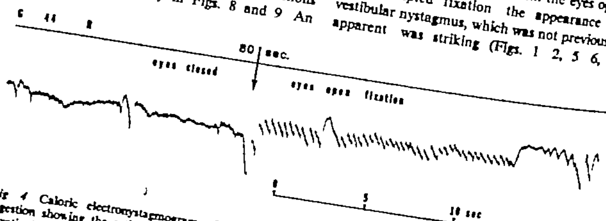
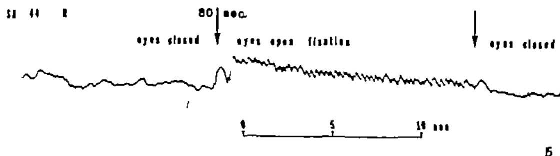
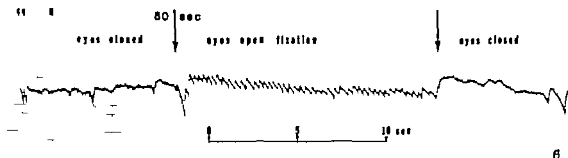


Fig 4 Caloric electronystagmogram after alcohol ingestion showing the activating effect of eyes open (fixation) upon the induced nystagmus.



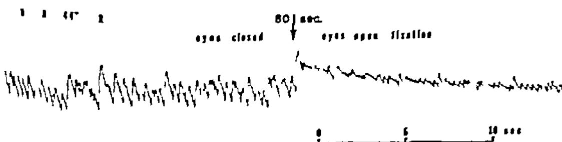


5 and 6 Caloric electronystagmogram after ...iturate ingestion showing the activating effect of ...s open (fixation) upon the caloric nystagmus. The ...agmus is not present or very faint and dysrhythmic when the eyes are closed and fixation abolished The subject was performing a serial seven subtraction task throughout the test.

...d 9). The activating influence of fixation ...een also after alcohol ingestion (Fig. 4) Thus, different results are observed in Tests ...4 and 5 (Figs. 3 and 7) Eye closure brings ... activation of nystagmus in all its fea... with the eyes open and fixating, an ...ibitory effect can be seen upon the induced ...us.

...at is therefore demonstrated here is a ...amic change in the form of the responses ... effect may be termed "fixation activation" of absent or diminished nystagmus, and the other "fixation inhibition" of previously present nystagmus.

The inhibitory influence of fixation on vestibular reactions is well recognized (Perlman & Case 1939 Aschan et al. 1956 Henriksson 1956 Collins, 1968 Sokolovski, 1963 1966 and many others) It has been shown that all features of the nystagmus are greatly reduced under the influence of fixation (Sokolovski 1963) Our results confirmed this. Weak nys-



...g. 7 Caloric electronystagmogram after amphetamine ingestion showing the inhibitory effect of eyes open (fixation) upon the nystagmus. Notice good nystagmus with eyes closed

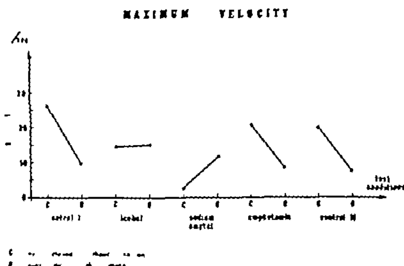


Fig 8 Group means, averaged across ears, of maximum velocity of postcaloric nystagmus expressed in degrees per second during eye closure (no fixation) and eye opening (fixation) conditions in the five test procedures.

tagmic responses were recorded in normal subjects when the fixation was introduced, whereas no-fixation and eye closure resulted in increased intensity of the caloric nystagmus.

If the nystagmus mechanism is dependent upon an interaction between vestibular nuclear neurons and reticular formation neurons, and if most of the vestibular impulses are conducted through the reticular formation (Gernandt, 1968) then the action of the specific drugs on the reticular formation should affect mainly the impulses funnelled through this pathway The impulses funnelled through the medial longitudinal fasciculus will be unaffected. This means that only the discharges able to elicit the slow phase are not blocked (Lorente de Nó 1933, 1938 Szentágothai 1950 McCabe 1965). This was the condition in our experiments with sodium amylobarbitone where, during eye closure and no fixation very little or no induced nystagmus was encountered the eyes being held in tonic deviation in the direction of the slow component. Yet clear nystagmus, with its slow and quick component appeared during eye opening and fixation. The intensity of this nystagmus, however was never equal to the intensity of the nystagmus with eyes closed in the same subjects, when not under the influence of amylobarbitone

Based on our data obtained from the tests carried out on the 8 normal subjects, it is postulated that, on eye opening (fixation), the reversal (quick phase) of the slow component

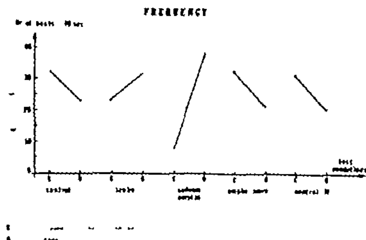


Fig 9 Group means, averaged across ears, of frequency of postcaloric nystagmus expressed in number of beats per 10 seconds during eye closure and eye opening conditions in the five test procedures.

the caloric nystagmus is acting along with e stimulation of attempted fixation. Conse ly summation of the two separate strong imuli opposing the slow component will re ilt in an inhibition of the nystagmus. Thus stagmus, if manifested, may be of more gular frequency but of smaller amplitude and er intensity

In our experiments with sodium amylobarbi the reticular formation, and therefore quick component of the induced nystag is believed to be blocked. However the al longitudinal fasciculus is unaffected able to conduct the slow component. efore the eyes would deviate in the direc of the slow phase and remain there On opening and attempted fixation the rapid movement toward the straight ahead posi swings the eyes back to the mid-line, but deviating force of the slow component is ill acting and so the nystagmic rhythm is stablished until the cupula can return to s zero position or upon eye closure when the rce of attempted fixation ceases to act, the ystagmus would disappear In a clinical rou ne this phenomenon of increased nystagmus ith eyes open and fixation is observed fairly equently and has been reported in connec on with posterior fossa lesions by Holmes 917), and later by others (Moberg et al., 962; Naito et al., 1963 Dix & Hallpike, 1966 edoux & Demanez, 1967 Hart, 1967 Coats, 970)

If then, eye closure with no fixation is as a standard state, eye opening and xation is found to have an inhibitory effect pon caloric induced nystagmus in normal ersons and an activating effect upon this ystagmus under the influence of the reticular ormation blocking drugs. We believe that it the attempted fixation which brings the ystagmic rhythm back.

It is our impression that the above electro- ystagmographic pattern might be of great iagnostic significance in brain stem lesions. ne might propose that the inhibition of the ystagmus during eyes open fixation be termed "Fixation Inhibition" (F.I.) and the enhance ment, or the recurrence, of the nystagmus previously not present, be called "Fixation Activation" (F.A.) The latter would be charac teristic of central vestibular lesion involving the brain stem—reticular formation, providing drug influence could be excluded, whereas the former pattern is indicative of normal ves- tibular function or of peripheral involvement if there is a vestibular disorder

ACKNOWLEDGMENTS

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ZUSAMMENFASSUNG

Untersuchungen über die steigernde oder hemmende Einwirkung optischer Fixation auf den kalorischen Nystagmus wurden durchgeführt. Acht normale Ver suchspersonen erhielten bithermale, kalorische Spülungen, um den Einfluss der Fixations- oder Nicht fixationsmethode unter verschiedenen Versuchsbe dingungen zu bestimmen

Folgende Beobachtungen wurden gemacht:

(1) Schliessen der Augen ohne Fixation hat steigernde Wirkung auf den Nystagmus von Normalpersonen und hemmt oder unterdrückt Nystagmus unter dem Einfluss von Drogen mit Hemmwirkung auf die retikuläre Formation.

(2) Öffnen der Augen und Fixation verringern oder unterdrücken den Nystagmus bei normalen Versuchspersonen und steigern oder reaktivieren den Nystag mus bei Personen unter Einfluss von Drogen, die die retikulare Formation blockieren.

(3) Man kann daraus schliessen, dass bei Durchführung kalorischer Tests der Nystagmus unter beiden Bedingungen — Augen geschlossen (keine Fixation) und Augen geöffnet (Fixation) — untersucht werden muss. Dadurch bekommt man wertvolle diagnostische Hinweise für die otoneurologische Untersuchung der Patienten.

Wird die elektronystagmographische Untersuchung dagegen nur bei geschlossenen Augen ausgeführt, können daraus leicht falsche Schlüsse hinsichtlich der estibulo-okulomotorischen Funktion gezogen werden.

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INTERACTION BETWEEN THE UTRICLES AND THE HORIZONTAL SEMICIRCULAR CANALS

III. *Sectioning of the Horizontal Ampullar Nerve on One Side and of the Utricular Nerve on the Other Followed by Tilting around the Longitudinal Axis*

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(Received October 30, 1973)

'ract In 70 cats selective sectioning of the hori- al ampullar nerve was performed on one side, of the utricular nerve on the other Sectioning he ampullar nerve caused nystagmus in the contra- ral direction. This nystagmus either decreased or ppeared completely as a result of the subsequent oning of the utricular nerve. Tilting toward the where the ampullar nerve had been cut resulted n increase in the previously diminished nystagmus, used its reappearance, if it had previously been bited. Tilting in the other direction caused no ation in those cases where inhibition had oc ed and total inhibition in those cases where agmus had been decreased. Finally if both cular nerves were cut there was no alteration in agmus during tilting in either direction.

semicircular canals and the otolith organs considered to perform different functions l are moreover also stimulated differently former by angular the latter by linear eleration. However they do not operate ependently of each other but seem to be mately coupled in their function (Maxwell 3 McNally 1955) In a previous paper the sent authors (Fluur & Siegborn, 1973) wed that in cats whose horizontal ampullar e and utricular nerve had been subjected unilateral selective sectioning tilting the mals around their longitudinal axis caused hange in the nystagmus, induced by the ration. Tilting toward the operated side ulted in increased nystagmus frequency reas tilting in the opposite direction caused inhibition. Hence, it was concluded that the intact utricle facilitates nystagmus brought about by the ipsilateral horizontal semicircular canal. This has given rise to a new problem which will be dealt with in this paper

What effect has the utricle on nystagmus induced by the contralateral horizontal semicircular canal?

MATERIAL AND METHOD

Twenty adult cats were used for the experiments. The operational- stimulative and re cording techniques are approximately the same as those described in our previous article (Fluur & Siegborn 1973). For sectioning of the utricular nerve not only was a fenestration performed but the bone was removed right down to the oval window so that the horizontal ampullar nerve was clearly visualized. The caudal parts of the oval window were also drilled off Thereafter the utricular nerve was approached by carefully drawing aside the horizontal ampullar nerve It is also important to limit the upper border of the utricular nerve against the anterior ampullar nerve. The nerve is dissected free with fine needles and c close to the entrance into its bony Great care must be taken not to pull i so that the membranous wall of

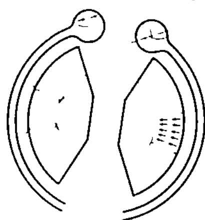


Fig 1 Schematic diagram of the utricles and horizontal semicircular canals in resting position after selective sectioning of the right horizontal ampullar nerve and of the left utricular nerve The arrows indicate the orientation of the hair cells, i e., the direction in which they increase their discharge frequency

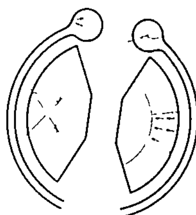


Fig 2 Schematic diagram of the utricles and horizontal semicircular canals after selective sectioning of the right horizontal ampullar nerve and of the left utricular nerve, when the animal is tilted to the right. Arrow indication same as in Fig. 1 The number of arrows symbolizes discharge frequency

becomes dislocated, thus damaging the entrance of the horizontal and anterior ampullae. The experiments were sometimes finished by cutting the nerve of the remaining utricle

RESULT

Selective sectioning of the horizontal ampullar nerve resulted in a destruction nystagmus toward the contralateral side when the animals had awoken to a level of superficial anesthesia. In six cats the subsequent selective sectioning of the contralateral utricular nerve (Fig. 1) gave rise to a considerable decrease in nystagmus frequency from about 15–25 beats/10 sec down to 4–10 beats/10 sec. In 14 animals, nystagmus was totally inhibited. In those subjects whose nystagmus frequency decreased

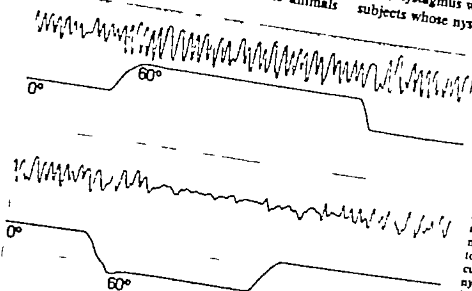
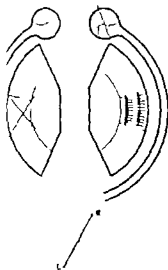


Fig 3 Consecutive curves from a cat after selective sectioning of the right horizontal ampullar nerve and of the left utricular nerve followed by tilting to the right. The upper curve shows electronystagmography and the lower curve the tilting of the table Tilting to the right upwards, to the left downwards.



4 Schematic diagram of the utricles and hori-... al semicircular canals after selective sectioning ... the right horizontal ampullar nerve and of the ... utricular nerve, followed by tilting to the left. ...w indications same as in Fig. 1 The number of ...ws symbolizes discharge frequency

...a result of the operation, tilting toward the ... where the ampullar nerve had been cut ...g. 2) increased the nystagmus frequency by ... beats/10 sec (Fig. 3). In two cases, tilting ...ard the other side (Fig 4) produced a de...ase in frequency of about 50% whereas ...our cases there was total inhibition (Fig. 3). ...n those cats in which the operation caused ...l inhibition of nystagmus it reappeared ...g. 5) during tilting toward the side where ... ampullar nerve had been cut, whereas on ...ng toward the other side, no nystagmus ... observed.

...mally in six cases the nerve to the re...ming utricle was cut. In those cats which had previously had a slow nystagmus a further decrease in frequency occurred, while ... where there had been total inhibition ... mus recurred with slow frequency ... these animals did not influence the ... of the nystagmus.

DISCUSSION

This operation creates a ... activity of the horizontal ... is missing on one side and ... that of the utricle is missing ... has shown that an increase ... "horizontal areas" of the ... brought about by tilting ... the nystagmus induced ... horizontal semicircular ... put from the utricle ... tagmus. These results ... a crossed inhibit... lateral utricle are ... obtained during ... tioning of the ... 1973) That they ... lateral utricle is ... tioning of the ... leased a nystag... further tilting ... y ... ut ... side ... was ... nput ... a ... al ... top ... mm ... from ... r the ... e s

Bei 20 Katzen ... tale N. ampu... N. utricul... N. ampull... nach der ... vermindert ... Abschnitt...



Kippung nach der Seite, wo der N. ampullaris abgeschnitten war, resultierte in einer Steigerung der zuvor herabgesetzten Geschwindigkeit des Nystagmus oder in einem Wiederauftreten bei vorherigem Schwund. Eine Kippung nach der anderen Seite hin erbrachte keine Veränderung in Fällen mit Nystagmusschwund, aber eine totale Inhibition in den Fällen mit herabgesetztem Nystagmus. Wurden schliesslich beide N. utriculares abgeschnitten, erhielt man keine Veränderung der Nystagmus durch Kippung.

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COCHLEAR MICROPHONICS RECORDED FROM THE EAR CANAL IN MAN

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By using average technique, cochlear micro-
ics were recorded from an electrode in the ear
l in response to 1 kHz-tone bursts, delivered
a μ-metal, magnetically shielded TDH 39 ear
in a closed acoustic system. No measurable
could be recognized, either in normal ears
deaf ears. The amplitude function is described
65 dB to 120 dB p.e. SPL and appears to be
ar to the established pattern in animals. The
of the cochlear microphonic was compared
the phase of the stimuli in the ear canal, and
influence of the stapedius muscle contraction on
itude and phase of the cochlear microphonic is
ly described. Besides the cochlear microphonics
the action potentials, a summating potential in
onse to 4 kHz-tone bursts was recorded. Cochlear
ics in a few pathological ears are outlined.
mately at a latency of 14 msec a multiphasic
ponent was often present. The results are dis-

ce cochlear microphonics (CM) were first cribed in animals (Wever & Bray 1930) y have been recorded in man by surgical thods from the round window (Perlman & se, 1941 Ruben et al., 1959) and also by -surgical methods (Yoshie & Yamaura, 9) Excellent literature reviews are found their papers.

CM are related to the physiological integrity the cochlear partition structures and can be as an indicator of the degree of hair cell pairment (Simmons & Beatty 1962) CM also be used to analyse middle ear trans- sion (Møller 1963) This paper concerns non-surgical recording of cochlear microphonics in humans by an averaging technique. The present paper will report findings at 1 kHz only where the CM are most readily recorded.

is work was supported by The Danish Medical Council.

METHOD

The recording techniques have been described earlier (Salomon & Elberling 1971 Elberling & Salomon, 1971) Differences from the previous reports were as follows: A 0.25 mm Teflon-insulated silver wire was placed with the chlorided tip in the skin of the ear canal next to the ear drum. A differential amplifier with 90 dB voltage amplification and a frequency response from 5–5 000 Hz was used. The input impedance was 1 GΩ and the common mode rejection, while using our electrodes, was greater than 120 dB. The equivalent input noise was 1.5 μV p.p.

1 000 Hz tone bursts were delivered via a TDH 39 earphone shielded in a cylindrical μ-metal case of 0.5 mm thickness. In the top and the bottom of the case two extra 1 mm μ-metal discs were inserted, separated from the case by copperfoil. The cable near the phone was also wrapped in μ-metal. The stimulus was a tone burst (normally 5 msec), which was measured using a 3-chamber artificial ear (B & K 4153) giving both the in dB p.e. SPL and the phase (Fig. 1). We previously shown the approximate l

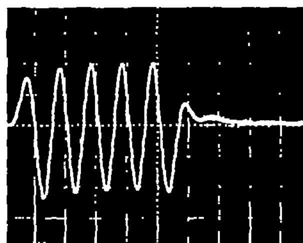


Fig 1 The 1 kHz, 5 msec tone burst stimuli, measured in a 3-chamber artificial ear (Brüel & Kjær type 4153). Time scale: 1 msec/div

tween measurements of transient sounds made in this way and with a corrected sound probe (Salomon & Elberling, 1971)

RESULT

1 *Evaluation of the μ-metal shielded ear phone*

In our previous paper (Salomon & Elberling, 1971) we used an iron-shielded TDH 39 ear phone which produced an artifact of 500–1 000 nV p.p at 1 000 Hz and 120 dB p.e SPL on deaf ears. This artifact, having a power function of 1 0 showed a decrease with increasing frequency Using the new magnetically shielded TDH 39 no artifacts could be detected in deaf ears. On testing the magnetic radiation from the μ-metal case a decrease of 26 dB at 1 000 Hz was found compared with the iron-shielded earphone. The absolute value of the magnetic field measured directly in front of the shielded earphone was 9×10^{-2} amp/meter at 1 000 Hz and 120 dB SPL and the shielding reduced the magnetic field by 45 dB compared with the bare TDH 39 earphone

2. *Measurement of CM in normal ears*

In normal adults the CM could be recorded from 65 dB to 120 dB p.e. SPL.

At 65 dB the CM reached measurable values of about 50 nV p.p. which was equal to the residual background noise after 2 000 averages. Steady tones are perceived 12 to 18 dB above the sensation of the corresponding 5 msec tone bursts at 95 and 0 dB SPL respectively (Pedersen & Elberling, 1972). The upper limit of the range studied thus corresponded to less than 110 dB SL.

Fig. 2 shows an example from a normal adult. From 65 dB to 90 dB p.e. SPL the amplitude function is almost linear but at 95 dB p.e. SPL the curve levels out. The CM reproduce the stimulating waveform at all intensities without appreciable distortion

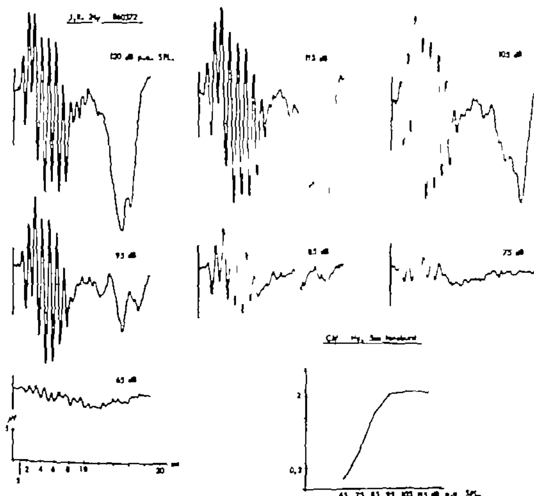
Fig. 3 also shows CM from a healthy person, but in this case the amplitude has a pronounced decrease at high intensity where a severe distortion of the CM is seen.

Fig. 4 shows the individual normalized amplitude functions from 5 normal persons, together with the mean curve. The mean amplitude curve shows a maximum at 105 dB p.e. SPL, a power function of 0.7 between 65 and 100 dB p.e SPL and a decrease in amplitude above 105 dB p.e. SPL.

At a latency of 1.2–2.0 msec the CM are distorted by the action potential from the inner ear and at a latency of approximately 14 msec a multi-phasic potential appears. This potential (see Figs. 2, 3 7) having a threshold of more than 80 dB p.e. SPL, shows decreased latency and increased amplitude with increasing intensity

Fig. 5 demonstrates the phase-shift between the stimulating waveform and the CM in one recording. The average phase-shift in six different persons was 110 ranging from 90 to 180

In 1959 Galambos showed that middle-ear muscle contraction elicited by contralateral sound-stimulation reduced the CM in cats, and Fig 6 shows that this is also the case in man. In a normal person the CM were recorded using 20 msec tone bursts, and the amplitude function was determined at 4 intensities. The reduced CM at 115 and 90 dB p.e. SPL caused by contralateral stimulation with 108 dB SPL



2. CM recordings and the corresponding ampli-
e function in response to 1 kHz, 5 msec stimuli
m a normal person.

te noise were recorded, and the new am- tude function is outlined. This amplitude nction indicates a 9 dB reduction in the chlear input.

Fig. 5 demonstrates that, besides the ampli- de reduction, a phase-shift is produced by ntralateral sound stimulation. In this re rding the shift amounts to 35

Summating potentials were small at 1 000 , but increased with increasing frequency g. 7 shows an example of this electro-nega- e potential recorded at 4 000 Hz.

Measurement of CM in pathological ears

pathological ears CM could also be re- rded. Recordings from a postoperative oto- sclerosis (high tone loss) and a Mondini-like defect (basal turn intact low tone loss) are shown in Fig. 8 A and B, as examples of cochlear localized lesions in either the high or the lower frequency range.

Fig. 8 C is from a patient with a flat 60 dB cochlear hearing loss (Menière)

In 5 severely deaf ears only small CM amplitudes could be recorded. An example is shown in Fig 8 D The amplitude functions having no maxima showed a great spread between the slopes.

DISCUSSION

The fact that the CM approximately d the stimulating waveform implies

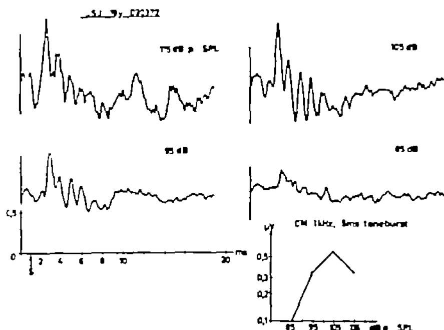


Fig 3 CM recordings and the corresponding amplitude function in response to 1 kHz, 5 msec stimuli from a normal person.

ficulties in differentiating the CM from artifacts. Electric and magnetic artifacts are approximately inversely proportional to the square of the distance between electrodes and sound transducer and Yoshie & Yamaura (1969) excluded artifacts using a distance of 30 cm. But in our instrumentation, proper shielding, high common mode rejection and low electrode impedance abolished any measurable artifacts, even when using a closed acoustic system on deaf ears. The electrode placement, avoiding contact with any acoustically active structures, did not give rise to mechanical artifacts, so that even when the vib-

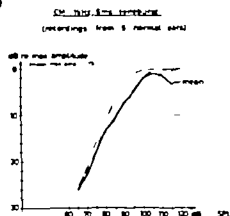


Fig 4 Double logarithmic plots of the CM amplitude functions from 5 normal persons, using 1 kHz, 5 msec stimuli (—). The individual curves have been normalized for comparison and the mean curve (—) is indicated.

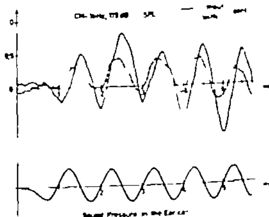


Fig 5 Phase relations of the CM waveforms. *Top* CM recordings from a normal person, using 1 kHz, 70 msec stimuli at 115 dB p.e SPL. Without (—) and with ( ) constant contralateral 108 dB SPL white noise stimulation. *Bottom*. Waveform and phase of the stimuli in the ear canal, measured in a 3-chamber artificial ear (Brüel & Kjær type 4153). A phase difference between the stimulus and the "normal" CM (—) of 96 (about 265 μsec) and a phase difference between the two CM curves of 35 (about 100 μsec) is calculated.

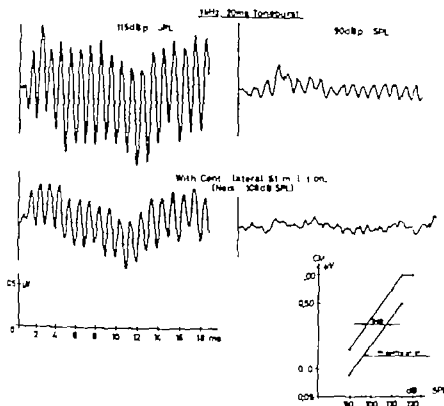


Fig. 6. Using 1 kHz, 20 msec stimuli at 4 intensities, in a normal person, the fig. shows (*top*) the recorded CM at 115 dB and 90 dB p.e. SPL. The calculated amplitude function (at 4 intensities) is shown (upper curve). *Centre*: CM recordings are shown at the same intensities, but with additional constant contralateral 108 dB SPL white noise stimulation (stapedius muscle contraction) giving a new amplitude function as shown (lower curve). The intensity shift between the two amplitude functions is about 9 dB as indicated.

...ation properties of the electrode were increased in one experiment by coiling the wire in the ear canal, no artifacts were seen in deaf ears.

The use of narrow band filters (Gavilan & ...anjuan, 1964 Ruben, 1967) and the use of cut-off frequencies closer than 2 octaves from the measured CM (Yoshie & Yamaura, 1969) have been avoided to allow proper measurements of the phase of the CM.

The nature of our recordings being genuine CM seems to be established by the power-function of the measured CM corresponding to the well-known non-linear amplitude function (Wever & Bray 1938) the phase angle between the stimulating sound in the ear canal and the CM corresponding to the values reported in animals (Møller 1963) and the fact that CM pick-up is changed in amplitude and phase by contralateral sound stimulation (stapedius muscle contraction).

By using both the so-called differential electrode technique (review Dallos, 1972) and a gross electrode near the round window in animals (Simmons & Beatty 1962) and in man (Yoshie & Yamaura, 1969) the recorded CM only reflect the cochlear generators within few mm of the electrode placement. An electrode in the ear canal with a more uniform distance to all parts of the cochlea, probably gives a more general picture of the overall cochlear functional state. Correspondingly the CM w... close to normal values both in a patient ... a pure cochlear high tone loss and ... tient with a low and middle frequ... lear hearing-loss (Fig. 8, curve

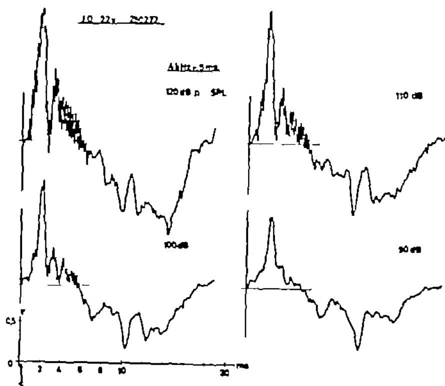


Fig 7 A negative summating potential recorded in response to 4 kHz, 5 msec tone bursts at 4 intensities.

whereas the CM were greatly reduced in patients where all frequencies were affected (Fig. 8, curves C and D). This seems to indicate that by using 1 000 Hz stimulation, the recorded CM provide information from any remaining normal part of the cochlea. This, combined with the fact that the CM are a logarithmic function with no threshold value, makes the clinical application difficult to assess.

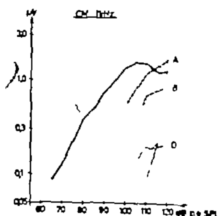


Fig 8 Normal and pathological CM-amplitude functions recorded at 1 kHz, 5 msec tone bursts. — mean, and dashed area, range covered by the recordings from 5 normal persons. results from pathological ears: A: postoperative otosclerosis with a cochlear high tone loss. B Mondini-like defect (basal turn intact) with normal hearing in the high frequency range (6–10 kHz) and severe cochlear loss in the low frequency range. C. Menière-disease with a flat cochlear hearing loss of 60 dB HL. D. a cochlear hearing loss exceeding 100 dB HL at all frequencies.

In ears with severe and widely distributed cochlear lesions the recorded CM were small. In these cases the CM recordings can be used clinically.

The late multiphasic potential appearing after the CM (Figs. 2, 3 7) is probably myogenic in origin. It has a latency of 10–15 msec, and it appears in shape similar to the responses reported by Kiang et al. (1963) and Bortanyi (1964). Like the sound-elicited stapedius muscle reflex, the threshold of the response is greater than 60 dB SL.

ZUSAMMENFASSUNG

Mit Hilfe der average technique wurden Cochlear mikrophonien — als Reaktion auf 1 kHz-Tonimpulse — registriert. CM wurden von einer Elektrode im äusseren Gehörgang abgeleitet. Die Reizung wurde von einem µ-Metall auf magnetisch abgeschirmte TDH 39

elephon in einem geschlossenen akustischen System herfuhrt. Sowohl bei Schwerhörigen als bei Normalhörenden konnten keine messbaren Artefakte erkannt erden. Die Funktion der Amplitude von 65 dB bis 20 dB p.e. SPL wurde beschrieben als Ähnelt der eigen, die bei Tierversuchen erzielt wurde. Die hase der Cochlearmikrophonien wurde mit der timulationsphase im Gehörgang verglichen, und der influss der Stapedinsmuskelkontraktion auf die hase und Amplitude der Cochlearmikrophonien urde kurz beschrieben. Ausser der Cochlearmikrophonien und der Aktionspotentiale wurde auch eine ummationspotentiale als Reaktion auf 4 kHz-Tonmpulse registriert. Die Cochlearmikrophonien bei einigen Schwerhörigen wurden erwähnt. Bei einer La ruz von ungefähr 14 msec ist oft eine mehrphasische omponente vorhanden gewesen. Die Ergebnisse wer en behandelt.

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VOCAL CORD FIXATION IN LARYNGEAL CARCINOMA

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Abstract Fixation of the vocal cord in glottic carcinoma is a poor prognostic sign. In a follow-up study of 134 patients with $T_2N_0M_0$ glottic carcinomas, only 55% of those with impaired mobility of the vocal cord survived 5 years, compared with 70% of those with normal mobility. In a separate study of 28 serially sectioned laryngectomy specimens, with a fixed vocal cord before surgery the main cause of vocal cord fixation was invasion of the thyro-arytenoid muscle. The more extensive carcinomas invaded other laryngeal structures, including the laryngeal framework. There was a very poor correlation between the pre-operative clinical assessment and the pathological findings. Over 50% of these cases were clinically underassessed, chiefly because of spread of the tumour outside the larynx. We have concluded that until better methods of clinical assessment are developed fixation of the vocal cord in glottic carcinoma is a contraindication to conservation surgery.

Fixation of the vocal cord has been regarded as a poor prognostic sign. Heise & Baylis (1966) found that 70% of the patients with $T_2N_0M_0$ glottic carcinomas with normal mobility of the vocal cord survived 5 years, compared with only 57% of those with fixation. Shaw (1965) Mårtensson et al. (1967) and Vermund (1970) presented similar figures. In order to test the validity of this concept, we studied the five year survival of 134 patients with $T_2N_0M_0$ glottic carcinomas treated in Toronto. Our study confirms the earlier reported results.

In addition we studied 28 serially sectioned laryngectomy specimens from patients who had fixation of the vocal cord at the time of operation. These cases were selected from a larger series of laryngectomy specimens that have been processed in the same manner. The purpose of this study was to review the causes of vocal cord fixation. We found, as did Kirchner (1969) in a similar series, that the main cause of vocal cord fixation was invasion of the thyro-arytenoid muscle by tumour. We also wanted to compare the clinical pre-operative assessment with the histopathological findings in these cases. Many of the tumours were clinically under-assessed because of inability to assess spread outside the laryngeal framework. Whereas there are differing opinions as to the advisability of performing partial laryngectomy in the presence of fixation of the vocal cord, in a recent study Kirchner & Som (1971) concluded that such a procedure could be performed in selected cases. From our study we think such a procedure ill advised, mainly because of the inaccuracy of the clinical assessment in these cases. This is particularly true following irradiation.

MATERIAL AND METHOD

In the Toronto area virtually all patients with laryngeal carcinoma are referred to the Prin-

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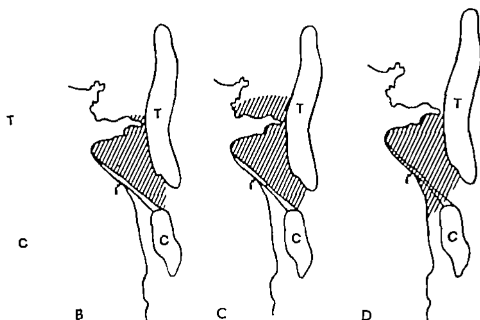


Fig. 1 Histopathological classification. Illustrations depicting: (*A*) glottic tumour confined to the glottic region; (*B*) glottic tumour with minimal supraglottic extension; (*C*) glottic tumour with supraglottic extension surrounding the laryngeal ventricle ("transglottic") and (*D*) glottic tumour with subglottic extension. *C* = cricoid cartilage. *CE* = conus elasticus. *T* = thyroid cartilage.

cess Margaret Hospital (a radiotherapy centre) for assessment before therapy This assessment is carried out by a radiotherapist and a laryngologist working as a team. The methods of assessment include indirect and direct laryngoscopy (more recently including microlaryngoscopy) suported by radiologic examinations (plane films, laryngeal tomography and a contrast laryngography). Most of these patients are treated by primary radiotherapy reserving operation for irradiation failure. However Bryce & Rider (1971) of Toronto recently studied a series of patients treated by

Table I. *T_2 glottic tumours—5 year absolute survival All modes of therapy*

	No of patients	No of survivors	survival	
One region, normal mobility	61	43	70	
One site, impaired mobility	40	25	63	55
One region, impaired mobility	33	15	45	

planned pre-operative radiotherapy followed by laryngectomy 6 weeks later

This oncologic centre, the Princess Margaret Hospital, maintains careful and complete follow up records, making it ideally suited for retrospective studies. In order to assess the prognostic significance of vocal cord fixation we reviewed 134 patients from the Princess Margaret Hospital with $T_2N_0M_0$ glottic carcinomas (classified using the UICC criteria 1968) For this portion of the study those patients having limited mobility without complete fixation of the vocal cord are grouped together with those having complete fixation of the cord. The period of study covered 35 years from 1930 to 1965 Most of these patients were treated by primary radiotherapy and we have a minimum five-year follow up on all patients. Of these 134 patients, 61 had nor vocal cord mobility and 73 had i mobility of the vocal cord. In the normal mobility the crude five was 70% In the group with im the crude five year survival



Fig 2. Spread outside larynx—thyro-arytenoid muscle invasion. Coronal section through a larynx at the level of the vocal process. The tumour (*arrows*) occupying the left glottic region, has extended subglottically and spread outside the laryngeal framework through the cricothyroid space with invasion of the upper margin of the cricoid cartilage (*C*). (Post irradiation.) *FC* = false cord. *T* = thyroid cartilage. *VC* = vocal cord.

II *Regional involvement. Invaded structures*

Structure invaded	Distribution of tumour (histopathological): Confined to glottic region (1)	Glottic with supraglottic extension (1)	Glottic with subglottic extension (6)	Glottic with supra- and subglottic extension (20)	Total (28)
Muscles					
Thyro-arytenoid	1	1	6	20	28
Lateral crico-arytenoid			3	16	19
Interarytenoid		1	1	9	11
Posterior crico-arytenoid				7	7
Crico-arytenoid joint		1	1	15	17
Perineural space				10	10
Thyroid cartilage			1	15	16
Spread outside larynx				16	18



Fig 3 Spread along muscle bundles. Horizontal section of a right partial laryngectomy specimen at the level of the vocal cord. The arrow marks the midline at the anterior commissure. The tumour has spread extensively along the muscle bundles of the thyro-arytenoid muscle beneath intact mucosa (postirradiation). C = cricoid cartilage. *T* = thyroid cartilage.

figures confirm that fixation of the vocal cord is a poor prognostic sign in glottic carcinoma ($p = 0.051$) (Table I).

In addition, we have had the opportunity of studying 110 laryngectomy specimens removed for carcinoma during the period 1966 to 1971 These specimens were examined by the method of whole organ serial sectioning (Tucker 1961 1963 Hyams, 1969) On the basis of the histopathology 73 of these 100 tumours were considered to have arisen in the glottic area. The remaining 37 tumours were either supra glottic, subglottic, or multiregional. Of the 73 patients with glottic primaries, 28 were considered, on clinical assessment, to have fixation of the vocal cord at the time of laryngectomy These 28 laryngectomy specimen form the basis for a detailed study of the causes of vocal cord fixation, and for a cor relation between the clinical assessment and histopathological findings.

Of the 28 primary glottic tumours, histopathologically one was confined to the glottic region (Fig. 1 *A*) one had slight supraglottic extension (Fig. 1 *B*), six had slight subglottic extension (Fig. 1 *D*), and 20 had both subglottic and supraglottic extension. The descriptive term "transglottic" refers to neoplasms which cross the laryngeal ventricle and involve at least the glottic and supraglottic regions (McGavran et al. 1961) (Fig. 1 *C*). Seven of our 28 tumours could be described as having a "transglottic" distribution. In the histologic assessment of these tumours, we considered the conus elasticus to be the boundary between the glottic and subglottic regions, and the lateral angle of the laryngeal ventricle to be the boundary between the glottic and the supraglottic region (Fig. 1).

Of the 28 patients in this study 10 were treated by elective surgery 6 weeks after a full course of radiotherapy (5 500 rads over 6 weeks), 6 had elective surgery following 500 to 2 000 rads immediately pre-operatively 10 were treated by surgery following irradiation failure (including one partial laryngectomy) and the remaining 2 patients were treated by primary surgery

In the irradiation failure group the length of time between the completion of irradiation and the surgical excision varied from 4 to 33 months.

Causes of vocal cord fixation as histopathologically

In all 28 specimens the carci vaded the thyro-arytenoid



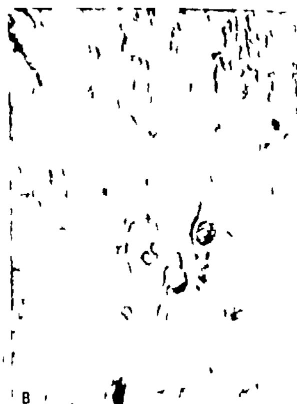


Fig 4 Impaired vocal cord mobility (*A*) Coronal section of the larynx at the level of the middle third of the vocal cords. Tumour (outlined by arrows) occupies the left vocal cord and extends subglottically (*S*). Note the absence of invasion of the laryngeal framework. *C* = cricoid cartilage. *T* = thyroid cartilage.

(*B*) Photomicrograph of the same case showing nests of a moderately well differentiated keratinizing squamous cell carcinoma infiltrating the thyro-arytenoid muscle. There is extensive fibrous connective tissue surrounding the tumour foci (postirradiation).

r greater degree. This appeared to be the ajor factor in producing fixation of the ocal cord. The degree of involvement of the other intrinsic laryngeal muscles, the crico-arytenoid joint, and the thyroid cartilage depended upon the extent of the tumour In some, there was also invasion of the perineural space. Many of the larger tumours had extended outside the laryngeal framework (Fig. 2) The details of the spread of these tumours are set out in Table II.

Invasion of the thyro-arytenoid muscle The degree of vocal cord fixation depends upon the extent of involvement of the thyro-arytenoid muscle This muscle was invaded in all cases with fixation of the vocal cord. (In 4 additional cases in which vocal cord mobility was limited without complete fixation, the tumour had only invaded the thyro-arytenoid muscle but had not extended to the deeper structures (Fig. 4).)

Tumour invasion of the thyro-arytenoid muscle has two distinct histopathological patterns. Many larynges including those who had salvage surgery for irradiation failure, had viable nests of infiltrating tumour scattered through the muscle (Figs. 7 8) In the remainder including the bulk of those treated by combined therapy there was extensive fibrous replacement of both the tumour and the muscle (Figs. 4 10). We also noted that once the thyro-arytenoid muscle had been invaded, the tumour tended to spread beneath intact mucosa along the length of the muscle bundles (Fig 3).





B



C



D

…e 3 Invasion of laryngeal muscles (*B* and *D* are from the same case, *A* and *C* from different cases.) (A) Coronal section through the tip of the vocal process showing tumour involving the thyro-arytenoid muscle and lateral crico-arytenoid muscle (*LCAM*) …rads prior to surgery) *C* = cricoid cartilage, *E* = epiglottis, *T* = thyroid cartilage. (*B*) C… through interarytenoid region show… interarytenoid muscle (*IAM*) and the … cartilage (*C*) (postirradiation). *T* … (*C*) Coronal section through the … showing invasion of the …



Fig 6 Perineural invasion. Photomicrograph of circled area from Fig 5 D showing perineural invasion.

Invasion of the other intrinsic laryngeal muscles. The next most frequently involved intrinsic laryngeal muscle was the lateral crico-arytenoid muscle (Fig. 5 *A*) followed by the interarytenoid muscle (Fig. 5 *B*). When this latter muscle was invaded the tumour often extended beneath intact mucosa to the opposite side The posterior crico-arytenoid muscle (Fig. 5 *C*) was infrequently involved and in each case the tumour was quite extensive.

Invasion of the crico-arytenoid joint In 15 of the 28 specimens the crico-arytenoid joint space was directly invaded by viable tumour (Figs. 5 *C* 8 *D*) Two of the patients with viable tumour in the joint also had an associated septic arthritis. In 2 additional cases the joint exhibited fibrous ankylosis suggesting that previously it had been involved by tumour Both of these patients had been treated with combined therapy Twenty-one patients had invasion of the arytenoid cartilage including all 17 of those with invasion of the crico-arytenoid joint.

Invasion of the perineural space Invasion of the perineural space (Figs. 5 *D* 6) was noted in ten specimens. Because the perineural space offers little resistance to tumour spread, tumour may travel considerable distances from

muscle (*PCAM*) and also invasion of the crico-arytenoid joint (postirradiation). *A* – arytenoid cartilage *C* – cricoid cartilage *T* – thyroid cartilage (*D*) Coronal section through the arytenoid region showing extensive invasion of the thyro-arytenoid muscle and cricoid cartilage (*C*). Circle indicates perineural invasion shown in Fig. 6 (postirradiation). *C* – cricoid cartilage. *E* – epiglottis. *H* – hyoid bone. *T* – thyroid cartilage



Fig 7 ... Coronal ... the ... deep ... invasion ... thyroid ... through ... into ... tissue ...

he main mass within that space without involving adjacent structures.

...asion of the thyroid cartilage and spread ...side the laryngeal framework. In 18 specimens the tumour had spread outside the laryngeal framework by direct extension (Figs. 7 ... In 15 of these (14 with supraglottic and subglottic extension and one with subglottic ...ion), the tumour also invaded the thyroid cartilage directly In the remaining three, the ...our penetrated the cricothyroid membrane or cricothyroid space without invading the thyroid cartilage. As might be expected, the invasion of the cartilaginous structures, and ...ension outside the larynx tended to be associated with the larger and more extensive tumours.

Clinico-patholog... ... and IV)

The present ... clinical assess... findings in lary... clinically we ... Failure to ... had extended ... (T) either ... 7 8) or the ... or through ... (Figs. 2, 7 ... assessment ... assessed clin... T_3). The ... extension) ... of the 28 ... ...ians ...

Table III *Comparison between clinical assessment and pathological finding*

Histopathological findings	Preoperative clinical assessment					
Tumour extension	Glottic	Glottic with supraglottic extension	Glottic with subglottic extension		Glottic with supra and subglottic extension	
	T	T	T	T_4	T	T
Confined to glottis					1	
Glottic with supraglottic extension					1	
Glottic with subglottic extension						
Confined to larynx	1		2		1	
Extending beyond larynx	1	1				
Glottic with supra- and subglottic extension						
Confined to larynx		4				
Extending beyond larynx		7	2	1	5	1

spread of the tumour The same poor correlation (25% correct) was encountered if the clinical assessment of the mucosal extension of the tumour was compared with the pathology findings. Neither did our strict criteria for subglottic extension in the histopathological examination influence the poor correlation figures. This part of the study illustrates the difficulties involved in correctly assessing the real extension of laryngeal carcinoma.

DISCUSSION

Fixation of the vocal cord in glottic carcinoma has proved to be a poor prognostic sign (Heise & Baylis, 1966 Mårtensson et al. 1967 Vermund, 1970) This fact has recently been recognized by the UICC (Union Internationale Contre le Cancer 1971) in its proposed alterations in the TNM classification of laryngeal carcinoma. In the present UICC classification developed in 1962 (UICC 1968) fixation of the vocal cord in glottic T_2 tumours does not change the classification. In the proposed alterations, fixation of the vocal cord will automatically classify such a tumour as T_3. Moreover a glottic carcinoma localized to one vocal cord but with fixation will also be included in this T_3 group (T_2 using current classification). Impairment of mobility will, however still be acceptable in the T_2 group. Similar alterations are anticipated by the American Joint Committee for cancer staging and end results reporting (AJC, 1971) Our study reinforces these proposals.

Fixation of the vocal cord which develops following the commencement of radiotherapy or after completion of radiotherapy is a particularly ominous sign. This development occurred in 5 of our patients, and in all, the fixation proved to be due to extensive viable tumour growth, sometimes beneath an intact mucosa (Fig. 8).

In glottic carcinoma the most important single factor in producing vocal cord fixation

Table IV *Comparison between clinical assessment and pathological finding*

Region involved vertical extension		*28*
Correctly assessed	8	
Incorrectly assessed	20	
Spread outside larynx deep extension		*18*
Assessed	2	
Not assessed	16	









ɛ 8 Extensive tumour beneath intact mucosa (post-radiation). (A B C and D are all from one case) (A) ross photograph of the larynx showing intact mucosa ith no obvious tumour (B) Photomicrograph of the ly well differentiated squamous cell carcinoma (Celloidin technique). (C) Coronal section rough region C (in 8 A) showing an extensive tumour volving the whole right vocal cord beneath a mainly [illegible] invades the upper portion of the cricoid cartilage and spreads through the cricothyroid space (S). C = cricoid cartilage. H = hyoid bone. T = thyroid cartilage. (D) Coronal section through region D (in 8 A) tumour deep to the arytenoid cartilage (A) sion of arytenoid and cricoid (C) cartilages. the tumour outside the thyroid cartilage (T) by the arrow Note tumour invasion of joint as well as crico-arytenoid joint. E





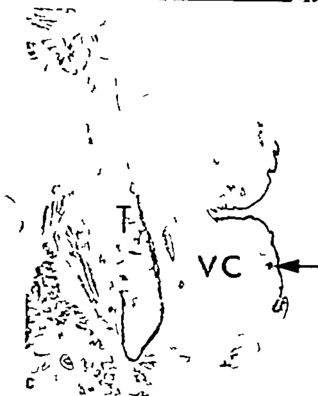




Fig. 9. Partial laryngectomy—Impaired mobility. (*A*, *B*, *C* and *D* are from the same case.) (*A*) Gross photograph showing a partial laryngectomy specimen with an ulcerated tumour in the posterior portion of the vocal cord. *C* and *D* mark the coronal sections 9 C and 9 D. (*B*) Photomicrograph showing a moderately well differentiated squamous cell carcinoma (post irradiation). (*C*) Coronal section (level *C* in 9 *A*) showing nests of tumour (*arrow*) beneath intact mucosa. *FC* = false cord. *T* = thyroid cartilage. *VC* = vocal cord. (*D*) Coronal section (through the visible tumour at level *D* in 9 *A*) showing destruction of the vocal process by tumour and subglottic extension to the level of the upper border of the cricoid cartilage (C). *T* = thyroid cartilage.



Fig. 10. Fixed vocal cord—partial laryngectomy postop. (A and B from the same case.) (A) Gross photograph of the larynx showing oedema of the right hemilarynx but intact mucosa. Arrow marks the level of coronal section 10 B (B) Coronal section showing partial fibrosis of the thyro-arytenoid muscle. The conus elasticus is fragmented (arrow) suggesting earlier subglottic extension (postirradiation). Circled area (inset) showing nests of tumour (viable?). C = cricoid cartilage. T = thyroid cartilage.

direct invasion of the thyro-arytenoid muscle tumour This was present in all 28 specimens in this study (In an additional four cases with limitation of vocal cord mobility without complete fixation, the thyro-arytenoid muscle was the only structure invaded by tumour (Figs. 4 9)

Kirchner (1969) also found that "vocal fixation indicates deep invasion of the thyro-arytenoid muscle by cancer which often reaches, and sometimes invades the thyroid la

When the invading tumour reaches the muscles of the larynx it tends to spread along longitudinal axis of those muscle fibres (Fig. 3) presumably the route of least resist This feature becomes particularly important in tumours involving the posterior commissure because they may extend beneath intact mucosa, across the midline, either in the submucosal layer or within the interarytenoid muscle (Fig. 5 B)

Invasion of the interarytenoid muscle has been noted as a cause of fixation by Kirchner (1969) In addition, in the review of 100 serially sectioned laryngeal carcinomas, Norris et al. (1970) found 10 carcinomas that invaded the interarytenoid muscle and 15 that invaded the space under this muscle.

Similarly invasion of the posterior crico-arytenoid muscle (Fig. 5 C), although it is infrequent (occurring in 7 of the tumours), is particularly important surgeon because, in these cases, he

residual tumour in the pharyngeal mucosa of the postericoid region. This feature has also ·e·n noted in other series (Kirchner 1969· Norris et al., 1970) Similarly Harrison in 1971 ·ointed out that if undetected, carcinoma will · left in the margins of the pharyngeal repair ·nd the recurrence will be placed above the toma"

In a high proportion of our patients (15 out of 28) the tumour directly invaded the crico-arytenoid joint spa (Figs. 5 *C* 8 *D*). In two more, the presence of fibrous ankylosis of the joint after irradiation ·erapy suggests pre vious tumour invasion I· their series of 100 serially sectioned specim·ns, Norris et al. (1970) reported 15 laryngeal carci·omas with joint invasion.

In the glottic carcinomas ·ith ·· and subglottic extension, a high ·r· · · ·vaded the thyroid cartilage and 16 spread outside the laryngeal making wide field laryngectomy ·s. 7 8)

We have been surp pointed by the extremely poor een the clinical pre-operative a ·e histo-pathological findings ·my spe cimens. The high pr· d cases in this series, in pa·t ·he very poor correlation b· · known tendency of these · deeply beneath intact mu· ··Gavran et al (1959) conclu· ommon for a carcinoma to b ·e when examined histologically ·ha ·ically ap-preciated" Similar diff· ulti· ·he clinical assessment have been noted b· l ·ker (1963) and may also be amplified by the pre-operative irradiation (Norris & Peale 1·66 Goldman et al. 1966)

The faulty assessment of the tumours in the vertical plane (extent of involvement of supra glottic and subglottic regions) despite the support of the radiological examination, further underlines the necessity of improvement in the diagnostic methods. These discrepancies have also been stressed by Olofsson et al. (1972)

Many *surgeons* believe that fixation of t· vocal cord in glottic carcinoma is a contr· indication for partial laryngectomy (Biller · al. 1970, 1971 Clerf et al., 1948 Kirchne· 1969· Leonard & Litton 1971 Norris · Peale, 1966 Shaw 1966). Some surgeons, how ever will consider partial laryngectomy on p· tients with limited vocal cord mobility (Bill· et al. 1971 Sisson et al. 1970). Kirchn· (1969) stated that "hemilaryngectomy and le· extensive operations carry a high risk of inad· quate removal of cancer in the case with · fixed cord"

More recently Kirchner & Som (1971) i· dicated that, in selected cases, cordal carc· noma with fixation might be amenable t· hemilaryngectomy They consider a subglott· *extension of 8–9 mm or involvement of the i·* ferior ventricular surface of the false co· renders the case unsuitable for partial laryn· ectomy They emphasize that posteriorly th· safety margin for subglottic extension is le· "The ultimate decision as to the feasibility o· hemilaryngectomy in any and every instanc· must be made after exposure of the lesion b· laryngofissure."

Partial laryngectomy was performed in on· of our cases (Fig. 3) In two additional case· conservation surgery could have been per formed instead of total laryngectomy if th· surgeon had known the extent of the tumo· at the time of surgery (Fig. 10). (In additio· two of our cases with limited mobility of th· vocal cord had partial laryngectomy (Fig. 9)

We believe that partial laryngectomy is con· traindicated in most patients with glottic car cinoma and a fixed vocal cord. We base th· conclusion mainly on the poor correlation be· tween the preoperative clinical assessment an· the pathological findings in these tumours, especially in cases with previous irradiation. We do not know how many of those cases reported by Kirchner & Som (1971) in their series of serially sectioned specimens had un-dergone irradiation before surgery

It is often impossible to assess correctly the submucosal or extralaryngeal extension of

ryngeal carcinoma. We hope that the m-
use of microlaryngoscopy in combina
with improved radiological examination
ll give us more accurate clinical assessment
the future.

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ZUSAMMENFASSUNG

mmbandcarcinome mit eingeschränkter oder aufge-
Stimmbandbeweglichkeit haben eine schlechte
Wir studierten 134 Fälle von $T_3N_xM_x$
mmbandcarcinomen. Von 73 Fällen mit einge-
ränkter oder aufgehobener Stimmbandbeweglichkeit
rden in 40 Fällen 5-Jahresüberlebungen erzielt,
in 55 . Von 61 Fällen mit normaler Beweglich-
erzielten wir in 43 Fällen die 5-Jahresüberlebung,
in 70%.

Außerdem wurden Serienschnitte von 28 Kehl
n mit Carcinomen untersucht, die durch Laryngec
mie entfernt worden waren. Der M. thyro-arytenoi-
eus war in allen Fällen von Carcinomgewebe in-
triert. Die größeren Carcinome haben auch andere
uren wie andere Muskeln, die Art. crico-aryte
oidei und das knorpelige Gerüst angegriffen. Wir
len schlechte Übereinstimmung zwischen klinisch-
tiver Klassifizierung und histo-pathologischen
rgebnissen. Mehr als 50% der Tumoren war klinisch
äoperativ „unterklassifiziert". Die Hauptursache
für war Ausbreitung von Carcinomgewebe außen
m knorpeligen Gerüst. Wegen der schlechten Mög-
chkeit einer richtigen praeoperativen klinischen Klas-
fizierung halten wir partielle Larynxchirurgie bei
mmbandcarcinomen mit unbeweglichem Stimmband
r kontraindiziert. Wir hoffen jedoch, daß verbesserte
linische und röntgenologische Untersuchungen in
ukunft bessere Möglichkeiten geben, Fälle für par
elle Larynxchirurgie auszuwählen.

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REHABILITATION AFTER LARYNGECTOMY

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bstract. Fifty patients have been assessed after ryngectomy 60% attained adequate vocal rehabilitan. Motivation was the principal factor determining ccess. Age and operative factors were found to ve no influence on voice· females were found to less successful in this respect. 55% returned to eir pre-operative employment, many to jobs re uiring good voice or strenuous physical effort. ypосmia, subjective and objective was noted this ten improved 6 months after operation. The presence f the tracheostome was found to be troublesome the majority of patients. Most patients suffered rom post-operative depression for 6 to 12 months, arital stability was unaffected. Radical neck dissec on was found to increase morbidity to a consider ble extent.

hristian Theodor Billroth performed the first aryngectomy for cancer of the larynx nearly one hundred years ago in 1873 recurrence and death occurred within one month. Further ases were performed over the ensuing years ut cures were uncommon and mortality was igh due to haemorrhage, sepsis, mediastinitis and bronchopneumonia (StClair Thomson 1939). Assessment of the number of laryng ectomies performed in modern times is difficult, although Snidecor et al. (1962) estimated that there were 15 000–20 000 laryngectomees alive in the United States.

A substantial proportion of patients who undergo laryngectomy will have been cured of their disease and will die of other causes. The degree of rehabilitation achieved by these patients and their role in modern society is of importance. The problems of vocal rehabilitation have received much attention other aspects of post-laryngectomy life have received less attention and assessments of overall re habilitation are scant. The purpose of this paper is to make such an assessment.

METHOD AND MATERIAL

Fifty patients who had undergone total laryng ectomy under the care of one of two surgeons at the Royal ational Throat ose and Ear Hospital, and who were still living in the area were questioned examined and tested by the author personally No patients defaulted Patients who had undergone pharyngo-laryng ectomy were not included

The series comprised 40 males and 10 females. Age distribution at the time of examination was as follows:

20–30 years	1 (female)
30–40 years	0
40–50 years	3 (1 female)
50–60 years	21 (3 females)
60–70 years	13 (2 females)
70–80 years	12 (3 females)

The youngest patient was a wom [illegible] of 28 she had undergone surgery [illegible] the age [illegible] of 2 The oldest was a woman of 78 she had under gone surgery at the age of [illegible] The oldest patient to have a laryngect[illegible] was 74 at the time of operation

The intervals betw[illegible] operation and exami nation were as follow

3–6 months 4 patients
6–12 months 7 patients
1–5 years 19 patients
5–10 years 16 patients
10–18 years 4 patients.

Four patients had signs of recurrent disease at the time of examination.

Ethnic origins

Anglo-Saxon, 47
Jewish, 1
Polish, 1
West Indian (negro), 1

Pre-operative visit by a laryngectomee

Twenty six patients had been visited by a laryngectomee prior to operation. Of these, 18 considered this visit to have been of considerable value to them. The remaining 8 were indifferent, with the exception of one who found himself actively discouraged by the visit. Some who did not have a pre-operative visit felt that this would have helped them. Few patients were seen afterwards by a laryngectomee other than by the occasional chance meeting or by meetings at a Laryngectomee club

Radiotherapy

Twenty-eight patients had undergone a full course of pre-operative radiotherapy

Operative details

All patients had Gluck Sorensen type incisions with lateral limbs where radical neck dissection was performed. Twenty-one cases had undergone radical neck dissection two of these being at a later date No patients had undergone bilateral neck dissection Operative notes, in the majority of cases, did not record details of reconstruction of the pharynx or cricopharyngeus muscle.

Pathology

Forty nine cases had suffered from carcinoma of the larynx. The histology was squamous cell carcinoma with occasional cases being reported as anaplastic carcinoma. One patient, a man of 45 had undergone operation for long-standing multiple papillomatosis.

Speech

An assessment was made of the patients' ability to communicate by oesophageal speech. Patients were divided into four categories falling into two groups:

Group A Adequate vocal rehabilitation. (i) Very good. superior speech resulting in fluent conversation with minimal intake gaps. (ii) Good. speech enabling conversation but with intake gaps.

Group B Inadequate vocal rehabilitation. (iii) Fair a degree of oesophageal voice allowing some vocal communication, but not allowing conversation Ability to make known needs in the home shops, etc. (iv) Poor little or no oesophageal voice. Communication by whispered voice, signs and written word.

Results

Group A (i) Very good, 7 (ii) Good, 23 total 30 (60%).
Group B (iii) Fair 12, (iv) Poor 8 total 20 (40%).

Relationship of results to particular factors

1 *Age* Average age of patients in Group A is 61 years. Average age of patients in Group B is also 61 years. Seven (23%) of the patients in Group A were over 70 years of age (at the time of examination) and 5 (25%) in Group B were over 70 years of age

2. *Sex* Three out of the 10 females fall into Group A

3 *Nature of surgery* Twelve out of 30 in Group A had undergone radical neck dissection (45%) compared to 8 out of 20 patients in Group B (45).

4 *Speech therapy* No relationship was evident between the number of attendances at speech therapy and the degree of oesophageal voice obtained. Many of the better speakers had had only few lessons.

5 *Pharyngeal bar* Thirty patients were noted to have a pharyngeal "bar" stretching from side to side across the pharynx at the base of the tongue (in a similar place to the normal epiglottis) In half these patients this bar was very marked. Eighteen out of the patients in Group A (60%) exhibited a pharyngeal bar Twelve out of those in Group B had a bar (also 60%). One patient had a tight pharyngeal bar and complained at the time of examination of dysphagia. The bar was shortly afterwards divided under general anaesthesia. Recordings of his oesophageal voice before and after revealed no change in his voice after this procedure His voice was considered good.

6. *Radiotherapy* No correlation was found between pre-operative radiotherapy and subsequent voice production.

Failures

An attempt was made to elucidate those factors which might have contributed to failure to attain adequate oesophageal voice.

1 Mrs N B., a 73-year-old woman (operated on at the age of 68), developed benign oesophageal stenosis requiring regular dilatation. She never achieved oesophageal voice.

2. Mr J R., a 75-year-old man (operated on at the age of 70) had previously had a cardio-vascular accident resulting in hemiplegia. His physical and mental condition was poor

3 Mrs H. L., a 60-year-old woman (operated on at the age of 57) had a hiatus hernia.

4 Mrs G L., a 48-year-old woman (operated on at the age of 47), initially achieved reasonable oesophageal voice but did not exhibit oesophageal voice at the time of examination It is probable that having attained voice she then rejected its qualities as being unfeminine.

5 Mrs R. W., a 28-year-old woman (operated on at the age of 25), never attained voice It is probable that she also rejected the voice.

Failure in the remaining cases was more difficult to analyse. The overwhelming impression was gained that the principal factor was lack of motivation. Only one case who failed to obtain voice expressed marked disappointment, this was case no 1 above in whom a definite organic cause for failure was found. The remaining patients appeared to accept their inadequate voice with comparative equanimity

Discussion

The results of assessment of speech rehabilitation by various authors are variable. This is not surprising in view of the subjective nature of the problem.

Hayes Martin (1963) estimates that less than 50% rehabilitate adequately Hunt (1964) reviewing 85 consecutive cases found 85.8% obtained "good" or "superior" speech. Murphy et al. (1964) reviewing 24 cases found 14 with adequate voice (58%) Robe et al. (1956) found 18 out of 32 to have adequate speech (56%). Putney (1958) reviewing 440 patients found a 62% success rate. The author's series with a success rate of 60% confirms the average findings of previous workers. There is no evidence in this series that age plays a great part in the degree of vocal rehabilitation. The figures suggest that females may be less successful in attaining good voice than males, although the figures are small. Putney (1958) however found two-thirds of the women in a series of 440 had inadequate voice and draws attention to the psychological factor involved. The low coarse tones of oesophageal speech tend to be distasteful and embarassing to many women, there is no evidence that any other anatomical or physiological factor is involved.

The nature of the surgery does not appear to influence speech. Results were as good in patients who had undergone radical neck dissection as in those who had not. Putney (1958) also found no operative factors involved He included consideration of skin incisions and the method of reconstitution of the pharynx he found radical neck dissection to have no influence on voice.

There does not appear to be any re ship to the number of attendances therapy classes. The tendency is

those with poor or slow speech to attend classes longer than those who rapidly develop good voice.

Little mention is made in the literature of the pharyngeal bar exhibited in 60% of the patients in this series. The results, however indicate that this bar is in no way related to the site of the pseudo-glottis.

The impression was gained that lack of motivation was the most important factor in the failure to obtain good speech The introverted patient who is retired from work and lives alone sees little point in persisting if speech is not rapidly acquired The patient with the over protective spouse may see little point in persevering (or occasionally may find it useful not to persevere) Some patients do not appear to exhibit the fortitude or industry *necessary to acquire good speech. In only a* handful of patients is there a possible pathological cause for failure

The vast majority of patients will benefit from a visit by a "good" laryngectomee prior to operation there are a few however who may be discouraged by such a visit, especially women. Post-operative visits, or early attendance at a laryngectomee club may be beneficial to many patients.

No patients in this series were using an [illegible] routinely few had tried one [illegible] is the author s experience that the electrolarynx can improve communication for inadequate speakers even to the point of intelligible telephone conversation The results of good oesophageal voice are, however generally *superior both from a practical and from a* psychological point of view

Symptoms attributable to aerophagia (flatulence distention and borborygmi) occurred in some patients to a minor degree but in no case were they very troublesome

One further aspect of speech deserves attention Deterioration in speech is occasionally the first sign of recurrence of disease usually a lymph node or mass of lymph nodes in the neck This deterioration has been observed in patients before the patient was aware of the recurrence and before the surgeon was able to detect it clinically The mechanism of this early deterioration is not certain.

Occupation

Results

Forty patients were in regular pre-operative employment. Twenty-two (55%) returned to the same occupation. The remainder modified or ceased work as follows.

Modified, as a result of operation 5
Changed, as a result of operation, 5
Ceased, as a result of operation, 3
Changed, reasons not directly related to operation 5

Of the 13 who had changed or ceased work as a result of the operation 5 stated their original job was too heavy 3 were unable to climb heights, 3 changed because their voice was inadequate, one found the atmosphere too dusty (a wood machinist) and one (a commissionaire) could not comfortably wear a high collar

Amongst those who returned to their original occupation some were particularly noteworthy

1 Mr S C., a 59-year-old man continued to work as a lorry-driver
2. Mr E. S., a 59-year-old man continued as a long-distance lorry driver
3 Mr L. N., a 58-year-old man continued work as an information officer for an aircraft firm His voice was in the very good category He would initiate discussions with new *clients by informing them why his voice* sounded unusual.
4 Mr J P., a 55-year-old man continued as a dock labourer for 5 years after operation.
5 Mr J S a 64 year-old man continued as a gardener
6. Mr H. T a 62 year-old man continued as a manual worker on the railways.

Discussion

It is clear that there are a number of occupational groups for which a laryngectomee is

resulted. These do not necessarily fall into categories in which voice use or heavy vocal effort is at a premium. A number of have continued to perform jobs that red these attributes. In this series the ly occupational situations that appeared pletely to bar a laryngectomee were dusty spheres and heights. The former will include a wide variety of manual jobs. The latter includes workers on scaffoldings, buildings and steeplejacks it is obviously unwise to employ people on such jobs who are not in prime physical condition.

It is perhaps surprising that only 3 patients found it necessary to change their occupations as a result of their voice. The degree of vocal rehabilitation achieved in some patients and the occupations that they continued to pursue is evidence that there are few occupations that cannot be followed by the successful oesophageal speaker if he so wishes.

There were no professional voice users in this series. It is obvious that such people (e.g. actors, singers and clergymen) will be unable to follow their professions in the manner to which they were accustomed.

The commonest stated reason for failure to return to work in the same capacity as before was that the work was too heavy In some cases this may well have been a genuine inability to continue physically strenuous work as a result of the nature of this particular operation. In other cases there is little doubt that the opportunity to cease work was taken.

In those cases where the operation had forced a change or cessation of work no cases of severe financial embarassment were found, although financial loss occurred in some cases. It would appear that the Welfare State successfully protected patients in this respect. This series is selective in that it includes only those patients cared for within the State Medical Service. There may be a tendency for patients in higher socio-economic groups, in whom change of occupation may result in relatively greater financial hardship to seek private care.

The results indicate that the vast majority of patients can, if they wish, return to full time occupations, often in circumstances which require regular voice use or strenuous physical effort although modification in the nature of the work may be beneficial.

Physical Capacity

Method and results

The physical capacity in forty-one patients was tested by lifting weights on a bar Results were extremely variable this is to be expected in a widely differing group of patients. The figures have no statistical significance and a control series was abandoned at an early stage. It may however be worth recording that 33 (80%) patients were able to lift a bar weighing 55 lb from the ground to a shoulder-high position using both arms. Twenty-three (56%) were able to lift the bar to an arms-extended-above-the head position Twelve (30%) were able to repeat the latter procedure with a 75 lb bar

Ability to lift weights of 35 lb or 55 lb with one arm to a waist-high position was assessed in 15 patients who had undergone radical neck dissection In 10 of these patients the figures were the same on both sides. In the majority of these patients there was obvious difficulty in attaining the same result on the side which had undergone a neck dissection. In the remaining 5 patients, 4 could lift 35 lb weights on the normal side but could not lift this weight on the operated side one could lift 55 lb on the normal side but only 35 lb on the operated side.

Many patients felt that their physical powers were reduced after operation. "Breathlessness" was a common complaint. Other patients took pride in being able to do as much after operation as before.

Discussion

The results suggest that a laryngectomee's physical capacity after surgery will not him from pursuing everyday activities are however no indication that

capacity is not reduced by the nature of the operation The extent to which lack of thoracic fixation affects physical power in man is still uncertain

There is evidence to suggest that there is little change in physical powers after laryngectomy (Coyne et al., 1968) Sustained physical effort involves cardio-pulmonary function There is no evidence that there is any significant change in these functions after operation. The complaint of breathlessness may indicate a greater awareness of the passage of comparatively cold, dry air in the tracheo-bronchial tree rather than an alteration in pulmonary function

The results in patients who had undergone neck dissection suggest that physical capacity is limited on the operated side.

Further work in this field is indicated.

Olfaction

Method and results

Thirty-two patients stated that their sense of smell was poorer after operation Eleven stated they had lost their sense of smell completely Four noticed no change. Two had no sense of smell before or after operation One noticed improvement after operation Many patients [illegible] total anosmia for about 3 to 6 months after operation with some degree of recovery at about this time

Tests were made using four substances in solution lemon cloves, peppermint and almond. Odour identification is unreliable and therefore odour perception was the only criterion used Patients were tested as follows: (1) Solutions of the above substances were held in front of the anterior nares for up to 30 sec. (2) Those patients who were unable to perceive two or more of the test solutions were subjected to two insufflations of similar solutions into the nasal cavities from a Rogers insufflator

Thirty-one patients (62%) were able to perceive two or more of the odours by method 1 Of the remaining 19 17 (a further 34%) were able to perceive two or more of the substances by method 2. Many of the patients who were able to perceive odours without insufflation into the nasal cavities were observed to perform inspiratory "sniffs" in the same manner as a normal person, although obviously the intake of air was through the tracheostome This was apparently helpful in perceiving the odour When the solutions were placed in front of the tracheostome there was no successful odour perception

Discussion

The results confirm that decreased olfactory acuity is noticed by the vast majority of patients after laryngectomy The increase in olfactory acuity on insufflation into the nasal cavities suggests that the hyposmia is simply due to diminished air-flow to the olfactory area. The majority of patients however were subjectively unable to perceive odours until at least 3 to 6 months after operation. Whilst an apparent anosmia might well be expected for some weeks after operation (in a patient who has more pressing problems to attract his attention) it is not clear why this should persist for as long as 6 months after operation. It may be that there is some alteration in olfaction during that time It suggests that there may be a compensatory increase in olfactory acuity after operation but that such compensation takes some months to occur

In some patients inspiratory "sniffs" appear to facilitate olfaction. It may be postulated that such movements, producing a negative intra thoracic and therefore a negative intra oesophageal pressure may in the absence of a normal cricopharyngeal sphincter result in the movement of a column of air which would result in a degree of air-flow into the nasal cavities.

Hyposmia after laryngectomy was reported by Henkin et al. (1968) They considered that the hyposmia was not related to air-flow they found that gentle nebulization into the nasal cavities did not improve olfactory acuity These findings are not confirmed in this series.

However all but six of Henkin's patients were tested within 6 months of surgery whereas 39 in this series were tested later than 6 months after operation. Henkin also commented on the subjective improvement in olfactory acuity at about 6 months in many patients.

A possible correlation was noted between the good oesophageal speakers and olfactory acuity 70% of the speakers with Group A voices were able to perceive two or more of the odours placed in front of the nares whereas only 35% of those in Group B achieved this success. This possible correlation may represent an increased ability to achieve air flow through the nasal cavities in the good speakers. It may however merely reflect the mental attitude of the patient who has achieved an overall greater degree of rehabilitation

The author can offer no explanation of apparent increased olfactory acuity in one patient other than a psychological one

The situation requires clarification and further pre and post-operative quantitative testing is indicated.

Respiratory Tract

Results

Nineteen patients complained of crusting in the tracheostome and trachea. Only 2 patients found this very troublesome The remaining 29 patients had little trouble with crusting, although most had a certain amount in the first few months after operation. This later *diminished. Cough, either dry or productive,* was troublesome to a varying degree in approximately 30% No patient gave a definite history of coryza and few felt that their susceptibility to upper respiratory tract infections was any greater after operation. Many patients had some degree of watery rhinorrhoea. On examination all patients exhibited the typical lilac coloured nasal mucosa associated with these patients.

Discussion

Despite the comparative paucity of complaints about the tracheostome with its associated problems of cough, sputum and crusting, an impression was gained that these symptoms constitute a considerable problem to many patients. The fact that few complained markedly probably represents an acceptance of its inevitability rather than a lack of awareness of its presence.

Psychological Problems

Nearly all patients admitted to some early anxiety and depression. In most cases this lasted for about 6 months. Nine patients described this depression as being severe and lasting up to 12 months. A few received medication from their general practitioners but no patients had been referred for psychiatric treatment.

Harrison (1970) has stressed how different ethnic groups may react in differing ways to the operation. Some groups may regard the procedure as mutilating and may refuse operation or possibly commit suicide when they have discovered its effect.

Marital problems

The majority of patients felt that operation had caused little change in their marriage. In *a few cases there was a feeling that the operation* had brought the partners closer One patient's marriage did break up This was probably attributable to other causes. One patient felt that his condition had produced some degree of estrangement from his wife. Twenty-*three patients had had regular sexual relations* before operation of these, 19 were able to continue these relations after convalescence Four did not continue their sexual relations after operation and attributed this, in part, to their operation.

It may be concluded that operation had no adverse effect on marital stability Similar conclusions were reached by Murphy et al. (1964).

Effect of Radical Neck Dissection

Twenty-one patients had undergone rac neck dissection. All these patients

of symptoms attributable to this part of the operation namely pain and stiffness in the supra-clavicular and shoulder regions, inability to lift objects on the operated side and inability fully to abduct the arm. Some complained quite bitterly of these symptoms. The section on physical capacity above provides some evidence on this subject There can be little doubt that a neck dissection adds considerably to the morbidity a morbidity that has perhaps been underestimated in the past. These facts should be borne in mind in considering prophylactic or elective neck dissections.

Worst Effect of Operation

Many patients had considerable difficulty in deciding what the worst effect of the operation was. The majority thought that the voice change was the worst effect and associated with this in many was the inability to laugh, sing or whistle. Some stated that the tracheostome was the most troublesome factor Others considered the effects of a neck dissection to be their biggest problem Sometimes it appeared that the worst effects were those that the patient had been least prepared for

Conclusions

There can be little doubt that total laryngectomy imposes a considerable physical handicap It requires changes in way of life and alters outlook In the same way that people may overcome other physical handicaps to a remarkable degree so may the laryngectomee. This requires courage and stamina, especially in the early stages. A large number of these successful laryngectomees are proud of their achievements and rightly so Given explanation, encouragement and optimism the laryngectomee can return to a full useful and enjoyable life

ACKNOWLEDGMENTS

The author is grateful to Professor D F N Harrison for encouraging him in this project and for allowing him to examine his patients, to Mr Anthony Rad[illegible] for allowing him to examine his patients, to Mrs Joyce L. Cook, Senior Speech Therapist for helpful advice and to Miss V Johns, Head Social Worker for advice and information.

ZUSAMMENFASSUNG

50 Patienten nach einer Laryngektomie wurden beobachtet. 60% erhielten angemessene vokale Rehabilitation. Motivation war der Hauptgrund für den Erfolg. Alter und operative Fakten hatten keinen Einfluss, allerdings waren die Ergebnisse bei Frauen weniger erfolgreich. 55% der Patienten nahmen ihre Beschäftigungen wieder auf die sie vor der Operation ausgeübt hatten, viele in Berufen, die eine gute Stimme oder anstrengende körperliche Betätigung verlangten. Geruchlosigkeit, subjektiver oder objektiver Art, wurde bemerkt, jedoch verbesserte sich dies oft 6 Monate nach der Operation. Die Gegenwart der Tracheostome wurde von den meisten Patienten als belästigend empfunden. Ein Grossteil der Patienten litt während 6-12 Monaten unter postoperativen Depressionen, die Stabilität der Ehen blieb jedoch unbeeinflusst. Radikale Halsdissektion (Zergliederung) wurde als besonders sterblichkeitsvermehrend empfunden.

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STIMULATION OF SYMPATHETIC NERVE FIBRES TO THE NOSE IN CATS

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Abstract The sympathetic innervation to the nose of the cat has been investigated by two methods. Venous flow from one nose cavity has been recorded as drops of blood and simultaneously the nasal patency from the same cavity has been estimated by a balloon technique. More than one sympathetic pathway giving decreased venous flow and increased nasal patency in the nose cavity has been demonstrated. Some of the sympathetic postganglionic nerve fibres travel in the vidian nerve together with parasympathetic preganglionic nerve fibres. When the vidian nerve was stimulated with low intensities and high frequencies the parasympathetic effects dominated. With high intensities and low frequencies, the sympathetic effects dominated. In one of 17 cats no sympathetic fibres were found in the vidian nerve. Other sympathetic pathways to the nose are discussed. Finally stimulation of the contralateral cervical sympathetic nerve affects the nose cavity

Vasomotor rhinitis is supposed to be caused by an imbalance between sympathetic and parasympathetic impulses to the vessels and glandular elements of the nasal mucosa with a relative overactivity in parasympathetic nerves during attacks (Golding Wood, 1961) The pathways of the autonomic nerves to the nose in man are not known precisely but are thought to be the same as in certain animals of which the cat has been most thoroughly investigated.

The parasympathetic preganglionic supply to the nose emerges from the brain stem with the facial nerve but after a short distance leaves it as the greater superficial petrosal nerve This nerve then enters the pterygomaxillary fossa and there the preganglionic fibres synapse with the postganglionic in the pterygopalatine ganglion. Through the pterygopalatine foramen the postganglionic nerve fibres travel to the vessels and glandular elements in the nasal mucosa.

According to textbooks in anatomy the sympathetic postganglionic nerve fibres from the superior cervical ganglion travel along the internal carotid artery leave it as the deep petrosal nerve then join the parasympathetic nerves in the pterygoid canal and accompany these to the nasal mucosa.

An exception to this distribution of the parasympathetic and sympathetic pathways was shown by Malcomson (1959) who found the ethmoturbinal area of the nose in the cat innervated via the ciliary ganglion.

The nerve in the pterygoid canal and in the pterygomaxillary fossa central to the ganglion is called the vidian nerve and as described above it consists of preganglionic parasympathetic and postganglionic sympathetic nerves.

The rationale to treat vasomotor rhinitis would be to cut the parasympathetic supply only but this requires intracranial surgery Golding Wood (1962) and other authors have, however made a vidian neurectomy that they have also cut the sympathetic nerves their results are described as good. / the reason for this? Is there a good

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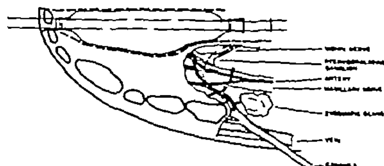


Fig. 1. A schematic drawing of the transpalatinal approach to the vidian nerve and the vein from the pterygopalatine foramen. The vein is marked with oblique lines and the artery is black. The nerves are unfilled.

tion of the sympathetic nerves and poor regeneration of the parasympathetic ones? Are there many pathways for the sympathetic supply to the nose? Are there any sympathetic fibres at all in the vidian nerve?

Malcomson (1959) has made experiments on cats indicating that the sympathetic supply reaches the nose via the vidian nerve. Jackson & Rooker however have recently (1971) called in question whether a vidian nerve section would remove a significant portion of nasal sympathetic fibres, at least in dogs. These authors have used similar recording techniques and have measured the pressure necessary to force a flow of air through the nose.

In the present investigation a new method is described, with which sympathetic pathways to the nose of cats were studied. The method implies that most of the venous flow from one of the nose cavities is measured in combination with pressure changes in a water filled balloon in the same cavity.

METHOD

The results in this report were obtained from 24 cats. The animals were given chloralose anaesthesia (80 mg/kg intravenously) after induction with ether. Additional doses were given when required. Breathing was ensured by inserting a tracheal cannula. The dissection of the pterygomaxillary fossa started with an incision in the buccal mucosa near the innermost tooth in the upper jaw. Under the mucosa a branch of the facial vein could be identified and traced just behind the tooth. Then the mucosa of the soft palate was deflected from the tooth to near the midline. The pterygoid muscle was removed carefully and under it the vidian nerve was seen and dissected free from adjacent tissue. The pterygopalatine ganglion was often concealed by the hard palate and in these cats some of the bone had to be drilled away. The vein was followed under microscope in retrograde direction to the pterygopalatine foramen. On the way to the foramen 7 to 10 branches of the vein were ligated, some of them much larger than the dissected vein. Fig. 1 is a drawing of the dissected region. A small water filled balloon was inserted in the nose cavity on the dissected side. The balloon consisted of a very thin latex tube with a diameter of about 8 mm tied at both ends over a polyethylene tube with an outer diameter of 1.6 mm. The length of the tied balloon was about 20 mm. The polyethylene tube had small holes within the balloon. The function of the polyethylene tube was to make the insertion into the nose cavity easier and to conduct the pressure changes in the balloon to a transducer and a polygraph. The system was closed but the resting pressure in the balloon could be set at any desired level from a pressure bottle. Except in some experiments the level was set to 6 cm of water above the nose cavity. The cervical sympathetic nerve on the same side was prepared and sectioned and then heparin was given. The arterial pressure was recorded in the femoral artery using a mercury manometer. The vein from the nose cavity was cannulated with a polyethylene tube of widest possible bore as indicated in Fig. 1 and the venous blood was conveyed to a drop

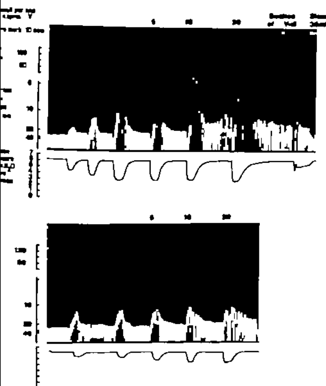


Fig 2 Cat, 3.2 kg. Responses to stimulation at various frequencies of the cervical sympathetic nerve before and after the vidian nerve has been cut. Stimulation periods and injections are marked underneath time record Lowest record represents balloon pressure manually transposed from the polygraph record. A decreased balloon pressure marks an increased nasal patency

mber with a photocell connected to an inate writer recording on a smoked drum. blood was returned to the cat by intra ous injections.

he peripheral end of the cervical sympath- nerve was stimulated with a unipolar trode. Square-wave pulses of an intensity of a duration of 3 msec and of various fre ncies were used. The peripheral end of vidian nerve was placed on a bipolar trode and the d ance between the two nts of contact was about 1 mm. The dura n was 3 msec and the intensities and fre encies were vari as described later

After the exp had been done and cat had beer by air intravenously nasal cavity w fully opened via the rd palate. Methyl blue solution was then ced in retrograd direction through the in order to map out the region sending od from the nose

Hexamethonium bromide and dihydroer tamine methansulphonate were administered travenously

RESULT

Stimulation of the cervical sympathetic nerve before and after section of the vidian nerve

The resting venous flow from one nose cavity varied between 10 and 30 drops per min in all cats, that is 0.5 to 1.5 ml per min. With an intensity of 4 V and with various frequencies the peripheral end of the cervical sympathetic nerve was stimulated in 11 cats. The nasal patency increased and the maximal responses were generally reached at 10 impulses per sec. Simultaneously the venous flow decreased, as can be seen in one example in Fig. 2. The responses in both records were larger before than after section of the vidian nerve, indicating that some of the sympathetic nerve fibres travel in the vidian nerve. But in all th there were marked responses w had been cut, indicating that ways to the nose other than in do exist. As can be seen in ferences before and after

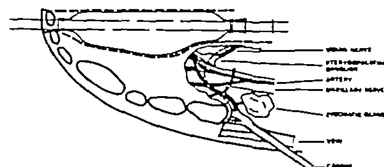


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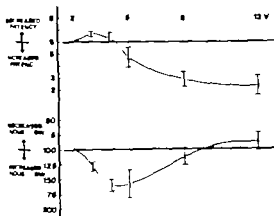
d not increase the nasal patency as also videnced in Fig. 3 The effect on the venous low was investigated in only 3 of the 8 cats. timulating the contralateral cervical sympathetic nerve gave a small but an obviously ecreased venous flow

timulation of the vidian nerve with arious intensities and frequencies

e peripheral end of the sectioned vidian erve was electrically stimulated in 17 of the ats. In 13 the intensities were varied from 2 o 12 V and in 5 of these the frequencies from 1 or 1 to 20 per sec. The effects of stimulat ng the vidian nerve with a constant frequency f 10 per sec and with various intensities can e seen as mean values (with S.E.M.) in Fig 4

e nasal mucosa never reacted at 2 V but s a rule at 3 From 3 to about 8 V the venous low was faster than the resting flow with a aximum at about 4 V From about 8 to 2 V the venous flow decreased on stimulation.

e nasal patency decreased from 3 to about V and over 4 to 5 V it increased. Thus the reversal" for the venous flow occurred at igher intensities than the "reversal" for the asal patency In order to investigate why the



ig 4 Responses to stimulation of the vidian nerve t a frequency of 10 sec and at various intensities. Mean values with standard error of mean from 13 cats. Ordinates from above: pressure in the balloons in cm f water above the nose, changes of the venous flow n percentage of the resting flow *Abscissa*: stimulaion in volts.

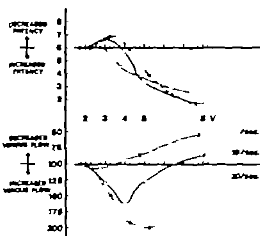


Fig 5 Responses to stimulation of the vidian nerve at various intensities and frequencies. Mean values from 5 cats. *Ordinates* and *abscissa* as in Fig. 4

two "reversals" were obtained at different intensities the outflow level of the falling venous drops and the resting pressure in the balloon were varied, but this made very little differ ence.

In one cat there was no sign at all of vasoconstrictor nerves in the vidian nerve.

In 5 cats both frequency and intensity were varied on stimulation of the vidian nerve. In all of them the same regular patterns could be seen for the venous flow At low fre quencies, for instance 0.5 and 1 per sec, the venous flow was lower than at 10 and 20 per sec at constant intensities. Stimulation at low frequencies gave, as a rule even slower flow than at rest except below 4 V where it gave an increased venous flow This indicates that the threshold for stimulation of the post ganglionic sympathetic nerve fibres in the vidian nerve at a duration of 3 msec and with the electrodes used lies at about 4 V The mean values of the 5 cats are given in Fig. 5 and as can be seen, the nasal patency did not change as regularly as the venous flow

Stimulation of the vidian nerve before and after a ganglionic blocking agent

After stimulating the vidian nerve elec

4 cats were given 5 mg/kg hexam

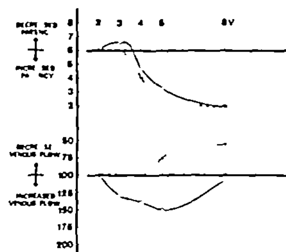


Fig. 6. Responses to stimulation of the vidian nerve at 10 sec and various intensities before (——) and after 5 mg/kg hexamethonium intravenously. Mean values from 4 cats. *Ordinates* and *abscissa* as in Fig. 4.

intravenously. The immediate effect of this ganglionic blocking agent was a fall of the blood pressure, a decrease of the venous flow and an increase of the nasal patency in all the cats. Five to 15 min later the nerve was again electrically stimulated at intensities from 2 to 8 V and frequencies from 0.1 to 20 per sec. The results were a decreased venous flow and an increased nasal patency. The differences before and after hexamethonium were largest at 10 to 20 per sec and least at low frequencies. Mean values of the 4 cats stimulated at a frequency of 10 per sec and at various intensities are given in Fig. 6.

Stimulation of the vidian nerve before and after an α-adrenergic blocking agent

Dihydroergotamine, a drug with α-adrenergic blocking effects, was given intravenously in doses of 0.1 to 0.5 mg/kg, sometimes 2 to 3 times to the same cat. As a rule the blood pressure fell markedly at the first dose and then rose very slowly for one-half to one hour to (for the experiment) acceptable values. When the blood pressure decreased the nasal patency always increased. The venous flow, on the other hand, did not always decrease. In some cats it did not change very much. Owing to the pronounced fall of the blood pressure, results were obtained from 4 cats only. The vidian nerve was stimulated with a frequency of 10 per sec and with intensities between 2 and 12 V. After dihydroergotamine the venous flow was higher for intensities over 4 V. The nasal patency decreased but not always for the highest intensities. The "reversal" for the nasal patency had not disappeared but changed place as a sign of incomplete sympathetic blockage. Mean values of the 4 cats are given in Fig. 7.

DISCUSSION

With methods reported in the earlier literature it has only been possible to measure the degree of nasal patency. A decreased nasal patency has been designated as vasodilatation and an increased as a vasoconstriction, but in this article it is preferred to avoid the terms of vasodilatation and -constriction. As we know that the system of vessels in the nose is very complicated and that there are large reservoirs for blood in the sinusoids, it is clear that changes in nasal patency and blood flow through the nose do not necessarily run parallel. The two methods described above offer the possibility to measure these changes simul-

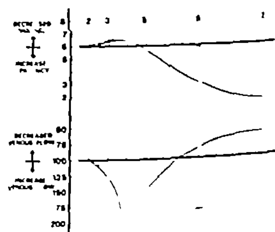


Fig. 7. Responses to stimulation of the vidian nerve at 10 sec and various intensities before (——) and after dihydroergotamine in doses of 0.1 to 0.5 mg/kg intravenously. Mean values from 4 cats. *Ordinates* and *abscissa* as in Fig. 4.

taneously But a comparison can be made only qualitatively and not quantitatively because there is no evidence that the collecting vein drains just the same part of the nasal mucosa as that covered by the balloon.

As early as in 1913 Tschalussow demonstrated decreased nasal patency after electrical stimulation of the vidian nerve in the cat and since then the existence of vasodilator nerve fibres to the nose has never been denied. The existence of nerve fibres in the vidian nerve giving an increased nasal patency has, however been more debated. Malcomson (1959) needed intensities of stimulation of more than 7 to 10 V to get an increased nasal patency in cats and Jackson & Rooker (1971) have suggested that such high intensities may give an irradiation to sympathetic fibres along vessels and sensory nerves in the vicinity The latter authors, working on dogs, found no or very few sympathetic fibres in the vidian nerve.

In this investigation the responses to stimulation of the cervical sympathetic nerve were significantly smaller after than before section of the vidian nerve, and just when the latter nerve was cut a brief reduction of the venous flow and an increase of the nasal patency appeared These results, together with the effects of direct electrical stimulation of the vidian nerve with and without a ganglionic and an α-adrenergic blocking agent, tend to prove the existence of sympathetic fibres in the vidian nerve in the cat. But as the responses to stimulation of the cervical sympathetic nerve after the vidian nerve was cut were very obvious in all the cats, other sympathetic pathways must exist. It is not possible, however with the present methods to estimate the proportions of sympathetic fibres in the different pathways. Furthermore, the proportions of sympathetic nerve fibres in different pathways do not seem to be the same from cat to cat, best exemplified by one of the cats in which no sympathetic nerve fibres at all could be demonstrated in the vidian nerve.

Sympathetic pathways other than in the vidian nerve have been proposed and demonstrated before. Malcomson (1959) stimulated nerve fibres central to and peripheral to the ciliary ganglion and got an increased nasal patency Only a small part of the nose, the ethmoturbinal area, is supposed to be innervated by these nerves. The blood to this area comes from the ethmoidal arteries and the venous blood probably leaves by adjacent vessels and not by the vein passing through the pterygopalatine foramen. Therefore, stimulation of nerve fibres passing or relaying in the ciliary ganglion probably does not affect the venous flow in the present experiments. Another and certainly not unimportant sympathetic pathway to the nose may be along the external carotid artery as proposed by Jackson & Rooker (1971)

Finally impulses in sympathetic nerve fibres from the contralateral side have an effect on the nasal patency There is probably an effect on the venous flow too the results from 3 cats point in that direction. Whether the sympathetic nerves cross the midline is not known.

If these results can be transferred to man there seems to be after sectioning of the vidian nerve and without regeneration, enough sympathetic nerve fibres to the nose to give a good vasoconstriction or increased nasal patency and this might explain some of the good results in vasomotor rhinitis after vidian nerve section.

Sympathetic nerve endings are richly represented around the veins of the nose in rat, guinea-pig rabbit and cat (Dahlström & Fuxe, 1965) An indication of the presence of sympathetic nerves to the veins is given in the present experiments by the very early brief increase of venous flow after electrical stimulation of the cervical sympathetic nerve After this increase, the prolonged decrease followed. During the whole stimulation, even in the early stages, nasal patency was increased. The early brief increase in venous flow was more often seen on cervical sympathetic stimulation befor than after the vidian nerve had bee tioned. But this can hardly be tak dence that sympathetic nerve f

veins prefer the vidian nerve to other pathways.

The effects on the nasal mucosa of stimulating the vidian nerve with various intensities and frequencies seem to be due to at least two important factors. One is that with growing intensities within certain limits, more and more nerve fibres of both kinds are activated. The other is that the two sets of autonomic nerves have different frequency and intensity-response curves. This has of course been obvious to other investigators but from the present experiments with a ganglionic and a sympathetic blocking agent it has now been demonstrated. The threshold for stimulating parasympathetic nerve fibres is about 3 V and more and more fibres are activated up to 4 to 5 V. The threshold for sympathetic fibres is about 4 V but even up to 8 V more and more fibres seem to be stimulated. At low frequencies of 0.1 to 1 per sec the sympathetic effects are dominant and at 10 to 20 the parasympathetic effects dominate.

ZUSAMMENFASSUNG

Die sympathische Innervation in Nasen von Katzen wurde mit zwei Methoden untersucht. In einem Nasenraum wurde die venöse Strömung durch die Bluttropfen registriert und gleichzeitig das An- und Abschwellen der Nasenschleimhaut mit einem eingeführten Ballon gemessen. Dabei stellte sich heraus, dass mehrere sympathische Bahnen vorhanden sind, die bei Reizung die venöse Strömung verändern und die Nasenschleimhaut abschwellen lassen. Ein Teil der sympathisch-postganglionären Nervenfasern läuft im Nervus Vidianus mit parasympathisch-präganglionären Nervenfasern zusammen. Bei Reizung des Nervus Vidianus mit schwacher Intensität und hoher Frequenz dominiert der parasympathische Effekt, dagegen bei hoher Intensität und niedriger Frequenz der sympathische. Bei 17 Versuchen war eine Katze, bei der keine sympathische Faser im Nervus Vidianus gefunden wurde, die einzige Ausnahme. Weitere sympathische Bahnen der Nase werden diskutiert. Reizung der kontralateralen zervikalen sympathischen Nerven beeinflusst die Nasenschleimhaut.

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ON THE ORIGIN OF LYMPHOID CELLS IN THE PALATINE TONSIL

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Abstract The origin of the lymphoid cell populations of the tonsil was studied by sublethal whole body irradiation of normal and thymectomized animals. Two clearly distinguishable cell populations appeared to be present in the tonsil a thymus-dependent population, situated in the interfollicular areas, and another presumably bone marrow derived lymphoid cell population, localized in the follicular structures. From the experimental data obtained, it is concluded that no fundamental difference exists between the lymphoid tissue of the tonsil and that of the regional lymph nodes in the adult animal.

In the immunological response two different elements can be distinguished dependent on the nature of the antigen. the plasmacellular reaction (humoral immunity) in which specific antibodies are formed and the specific cellular reaction (cellular immunity) in which committed lymphocytes are involved.

The course of the plasmacellular reaction has been described by Fagraeus (1948) She demonstrated that antigenic stimulation gives rise to large basophilic blast cells, which are transformed into mature plasmacells. During this process a sharp rise in circulating antibodies, produced by these cells was observed. The origin of the precursor cells of this reaction is in the bone marrow as has been demonstrated by Balner & Dersjant (1964) Miller & Mitchell (1968), Nossal et al. (1968) and Miller & Mitchell (1969)

The specific cellular reaction is also accompanied by the formation of large basophilic cells but transformation in plasma cells does not occur The end cells of this reaction are small lymphocytes (Gowans et al., 1963 Oort & Turk, 1965). These cells are involved in the cell-mediated immune reactions such as homograft rejection, delayed hypersensitivity and sensitization by chemical substances like DNCB (Gowans et al., 1963 Keuning, 1965 Turk & Oort, 1969) It has been shown that mature thymocytes are the immunologically component cells in the specific cellular immune response (Miller 1962, Keuning & van den Broek, 1968 Veldman 1970).

In recent years experimental procedures have been developed facilitating the separation of these two elements of the immune response. Keuning & van den Broek (1968) subjected adult rabbits to repeated sublethal X-irradiation to eliminate temporarily nearly all lymphoid cells. To prevent the regeneration of the thymus-derived population of lymphoid cells, the animals were thymectomized before irradiation. In these animals the restoration of the antibody-forming capacity simultaneous with the reappearance of the follicular structures was observed 7–8 days after the last irradiation. However no repopulation of the paracortical areas in the regional lymph node occurred, while the potency for homo rejection was abolished throughout an o tion period of more than 100 days. parable experiments in which thym was applied, no significant loss o

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was observed in the paracortical areas of the regional lymph nodes, while the capacity for homograft rejection was not affected (Veldman 1970) The restoration of the antibody forming potency was the same as in the thymectomized animals. In this way a clear morphological and functional separation between the two different elements in the immune response could be obtained.

On the role played by the palatine tonsil in the immunological system there is a large diversity of opinions. Several hypotheses have been put forward, as for instance that the tonsil is an antibody-producing organ (Meyer zum Gottesberge & Koburg, 1967 Surján & Surján 1970) or an equivalent of the central lymphoid organs as the thymus (Harrison, 1970) or the bursa of Fabricius (Fichtelius, 1968)

The present report deals with an experimental study on the tonsil in which the origin of the lymphoid cell populations was traced with the use of the above-mentioned techniques and thus to obtain more insight into the role played by the tonsil in the immunological defense mechanism

METHOD

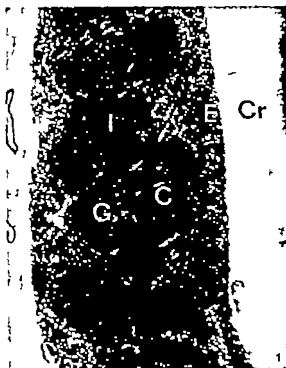
The experiments were performed on adult white rabbits of the New Zealand strain (about 3 kg body weight) For whole body irradiation a source of radioactive Cobalt^{60} was used. During irradiation the animals were fixed in a wooden box. A sublethal dose of 450 rads was administered three times at biweekly intervals. The radiation dosage was measured in the midline of the animal and administered in two equal amounts, one half to the left and the other half to the right side of the body Thymus shielding was performed with the aid of lead blocks.

For thymectomy endotracheal anesthesia was given, using a closed system through which a mixture of halothane nitrous oxide and oxygen was administered. Artificial respiration was started after opening the thorax by severing the first two ribs from the sternum. The exposed large thymus lobe was removed from the mediastinum by blunt dissection as well as the small cranial extensions along the carotid arteries. Subsequently the ribs, the muscular layer and the skin were sutured. Irradiation of these animals was started about 4 weeks after the surgical procedure

At various times after the last irradiation the animals were killed by intravenous injection of a lethal dose of Nembutal. In the thymectomized animals the thymus region was carefully inspected for the presence of thymus remnants. In none of the animals was any thymus remnant observed. Tonsils and popliteal lymph nodes were dissected, fixed in Zenker's solution and embedded in paraffin wax. Serial sections (7 μm) were stained with methylgreen-pyronine

RESULT

Micrographs of the structure of the normal palatine tonsil and popliteal lymph node of a young adult rabbit are shown in Figs. 1 and 2. The tonsil consists of a simple epithelial crypt. The epithelium is usually infiltrated to a varying degree by phagocytotic and lymphoid cells. Just below the epithelial layer a single row of follicles is arranged, with their lymphocyte corona directed towards the epithelium. This corona consists mainly of small dark-staining lymphocytes with scattered phagocytotic cells. The germinal centres, situated below the corona and revealing many mitotic figures, are populated by medium sized lymphocytes, blast type cells and phagocytotic cells. Between the follicles large accumulations of small lymphocytes and many epithelioid venules are observed On its outer side the tonsil is surrounded by a large mucous gland. Normally the ducts of this gland open into the pharynx, but sometimes openings are found into the crypt (Fig 3) The popliteal lymph node shows the normal characteristics of regional lymph nodes with a central marrow space, surrounded by follicles and the so-called paracortical areas





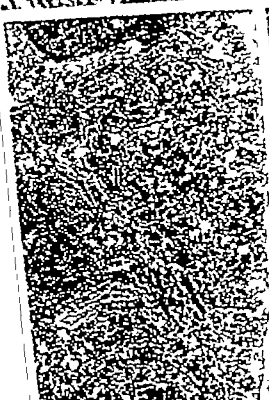


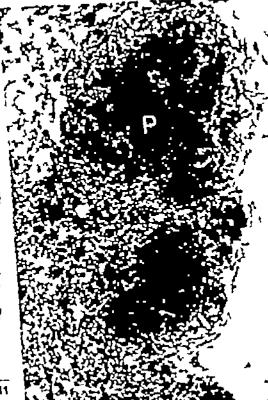


Figs. 1 2 Tonsil (Fig. 1 60) and popliteal lymph node (Fig. 2 40) in the normal adult rabbit. *C* lymphocyte corona, *Cr* crypt, *E* epithelium, *G* germinal center *I* interfollicular area *P* paracortical area, *F* follicle, *M* medulla

Figs. 3 4 Tonsil (Fig. 3, 40) and popliteal lymph node (Fig. 4 40) 6 days after the last whole-body irradiation of previously thymectomized animals. the difference in follicular repair between tonsil lymph node Interfollicular areas and areas depleted of lymphocytes. *D* opening gland duct into the crypt. *GL* mucosa







Figs. 9, 10 Tonsil (Fig. 9 130) and popliteal lymph node (Fig. 10, 60) 3 days after the last whole-body irradiation with thymus shielding. Clear lymphocyte accumulations in the interfollicular areas of the tonsil (I) and the paracortical areas of the lymph node (P). Follicular structures (F) in the tonsil already reappearing (immunoblasts), in the lymph node absent.

Figs. 11, 12 Tonsil (Fig. 11 130) and lymph node (Fig. 12, ×80) 6 days after the last whole body irradiation with thymus shielding. Large lymphocyte accumulations in the interfollicular areas of the tonsil (*I*) and the paracortical areas of the lymph node (*P*). *F* follicle.









Figs. 5, 6. Tonsil (Fig. 5, ×50) and popliteal lymph node (Fig. 6, ×50) 4 weeks after the last whole-body irradiation of previously thymectomized animal. Normal follicular structures. Interfollicular areas and paracortical areas however without lymphocyte accumulations.

Figs. 7, 8. Tonsil (Fig. 7, ×80) and popliteal lymph node (Fig. 8, ×40) 10 weeks after last whole-body irradiation of previously thymectomized animal. Absence of lymphocyte accumulations but normal follicular structures.

-ulations of lymphoid cells in the tonsil. validity of the used experimental proce- e can be concluded from our comparative ings in the popliteal lymph node The ob-ed separation of the two populations of phoid cells in this organ are in close agree- t with those described by Keuning & van Broek (1968), Nieuwenhuis et al (1970) l Veldman (1970)

The conclusion is drawn that a thymus-ded population of lymphoid cells is lo- ed in the well defined interfollicular areas the tonsil. The follicular structures contain econd non-thymus-dependent population y temporarily eliminated by the irradiation edure. About the origin of this latter popu- n of lymphoid cells it is tentatively as- ed that these cells originate from the bone row as has been demonstrated for the icular structures of the popliteal lymph de and the spleen (Balner & Dersjant, 1964 ning & van den Broek, 1968 Veldman 70).

According to these findings the tonsil seems be fully comparable to the regional lymph des and the spleen. Although no definitive of is given by these experiments, these two omically separate lymphoid cell popula ns in the tonsil can be supposed to cor spond to the two different elements in the munological system, the plasmacellular reac n and the cell-mediated immunity as has en demonstrated in the regional lymph nodes uning & van den Broek, 1968 Nieuwenhuis al, 1970 Veldman, 1970)

Confirmation of the immunological role of e two different cell populations by the plication of suitable antigens, provoking a cific reaction in one of the systems, is ther difficult, since the tonsil is continuously posed to antigenic stimulation. The presence blast-type cells in the follicular structures d the interfollicular areas shortly after the al irradiation might be attributed to this aneous antigen supply In this way the e difference in time between the restora of the follicular structures in the tonsil and the ly node nich 1 week only a sing ondary llicle bserved might be ex d

Apart fro te l pro the existence of a a pla llula re tion in the tonsil se the presence of numbe p in the epithelium outc borde lymphoid tissue Besid support t this assumption can be deri from the ments of Surján Surján (1970) & Patt (1971) ese author substantial p duction o bacterial antigens d of tonsillar tissue

The above consid the conclusion that from and a functional point o the adult animal dee from the regional l the tonsil might pl together with the lymphoid tissue, as is the first to be ex tion after birth

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ZUSAMMENFASSUNG

An normalen und thymektomierten Kaninchen wird mit Hilfe subletaler Ganzkorperbestrahlung die Herkunft der lymphatischen Zellen in der Tonsille untersucht. Mit dieser Technik konnten zwei lymphoide Zellpopulationen verschiedener Herkunft nachgewiesen werden. Eine vom Thymus abhängige Population konnte in den interfollikulären Gebieten lokalisiert werden. Eine zweite wahrscheinlich vom Knochenmark abhängige Population zeigte sich in den follikulären Strukturen. Diese Beobachtungen scheinen die Behauptung zu rechtfertigen, dass es bei erwachsenen Tieren keine fundamentalen Unterschiede zwischen dem lymphatischen Gewebe der Tonsille ... regionalen Lymphknoten gibt.

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